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REFERENCES: 1. Montero, A. C.; Rochelle, J. B., III, and Ford, R. V.: New England J. Med. 260:872 (April 23) 1959. 2. Fuchs, M.; Bodi, T., and Moyer, J. H.: Am. J. Cardiol. 3:676 (May) 1959. 3. Fuchs, M., and others: Monographs on Therapy 4:43 (April) 1959. 4. Montero, A. C.; Rochelle, J. B., III, and Ford, R. V.: Am. Heart J. 57:484 (April) 1959. 5. Rochelle, J. B., III; Montero, A. C., and Ford, R. V.: Antibiotic Med. & Clin. Ther. 6:267 (May) 1959. LITERATURE AVAILABLE ON REQUEST

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The American Journal of Medicine

Vol. XXVIII JANUARY 1960 No. 1

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The Kidney in Health; The Nephron in Disease
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Clinical Studies

Renal Tubular Disease with Muscle Paralysis and Hypokalemia
EDWARD E. OWEN AND JOHN V. VERNER, JR. 8

A report of unusual interest which gives an account of ten cases of renal tubular acidosis in which the clinical course was dominated by episodic muscle paralysis due to hypokalemia. A variety of other manifestations are described, some new or but rarely recorded previously, such as a "hyperdynamic circulation" in some instances, tetany, associated urinary sodium loss, and unusual manifestations of muscle weakness due to hypokalemia; osteomalacia was conspicuously absent in this series. Appropriate electrolyte replacement therapy was as successful as it usually is in these cases. A lonog term follow-up, over five years in six of the patients, disclosed no overt further renal d eteriration.

Periureteral Fibrosis, with a Diabetes Insipidus-like Syndrome Occurring with Progressive Partial Obstruction of a Ureter Unilaterally
DONALD KNOWLAN, MICHAEL CORRADO, GEORGE E. SCHREINER AND ROGER BAKER 22

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Chronic Idiopathic Jaundice. A Study of Two Afflicted Families
ROBERT L. WOLF, MURRAY PIZETTE, ALEXANDER RICHMAN, DAVID A. DREILING, WALTER JACOBS, OSCAR FERNANDEZ AND HANS POPPER 32

While genetic transmission and hence familial occurrence of chronic idiopathic jaundice (Dubin-Johnson syndrome) has been generally assumed, the evidence for this assumption has been scanty. The present study provides additional data on this point, and illustrates the variation in expressivity

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of the metabolic error which is presumed to underlie the disorder. Low orders of involvement occur which are difficult to recognize clinically and by laboratory study or even by close examination of the liver biopsy specimen.

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JANE F. DESFORGES, JEAN D. ROSS AND WILLIAM C. MOLONEY 69

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*Miller, J.B., et al.: Ann. Allergy, 12:611, Sept.-Oct., 1954.

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NEAL S. BRICKER, PETER A. F. MORRIN AND S. WESLEY KIME, JR. 77

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Clinicopathologic Conference

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Because of the infrequency of the disease in this age group, its sudden onset, the profusion of inconsistent presenting symptoms, and because the accompanying symptoms of anorexia and vomiting are also characteristic symptoms of many other ills of infancy.

Source: Traisman, H. S.; Boehm, J. J., and Newcomb, A. L.: Diabetes *8*:289, 1959.

for those pediatric puzzlers..."A routine urinalysis and blood sugar should be done whenever the possibility of diagnosing diabetes is entertained."*

DIABETES MELLITUS AT AGES 1 TO 5

Order of Frequency of Presenting Symptoms in 110 Patients

Symptoms	No. of Patients	Per cent of total group
Polyuria	93	84.5
Polydipsia	89	81.0
Weight loss	47	42.7
Polyphagia	28	25.4
Anorexia	16	14.5
Lethargy	14	12.7
Enuresis	7	6.4
Vomiting	5	4.5
Irritability	3	2.7
"Craving for sweets"	3	2.7
"Sticky diaper"	3	2.7
"Strong odor to urine"	2	1.8
Glycosuria	2	1.8
Hypoglycemia	2	1.8
Personality change	1	0.9
Boils	1	0.9
Headache	1	0.9
Abdominal cramps	1	0.9

Adapted from Traisman, H. S.; Boehm, J. J., and Newcomb, A. L.*

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Isolated congenital pulmonic valvular regurgitation is a rare clinical entity and, as in this case, is usually symptomatic. The lesion was securely established by precise cardiac catheterization and angiocardiographic technic.

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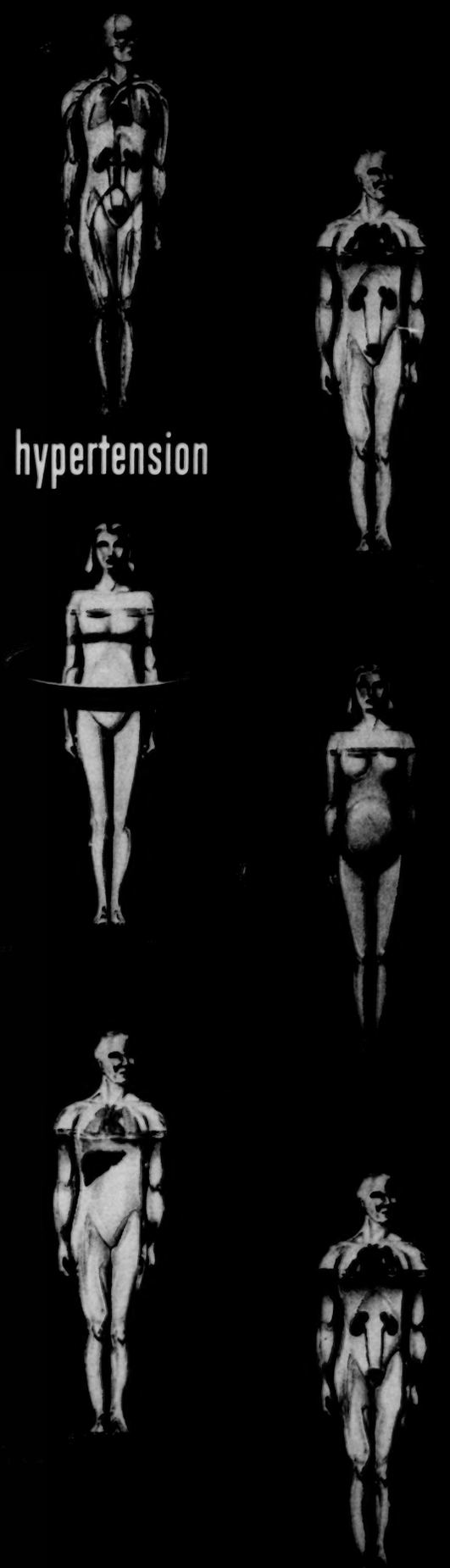
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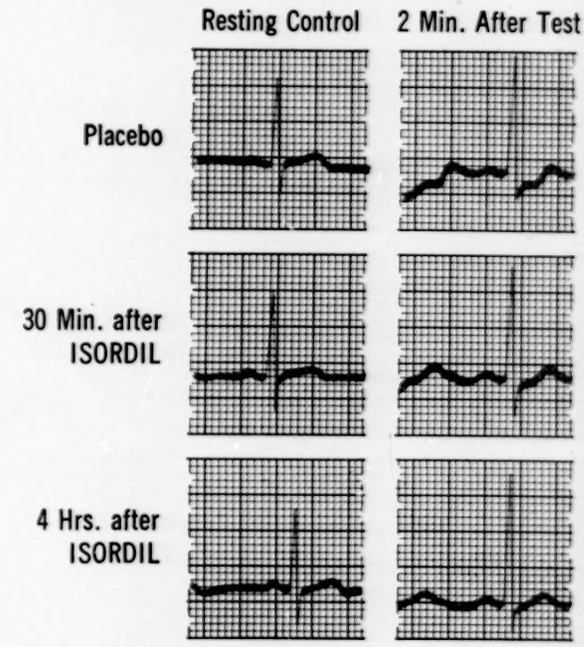
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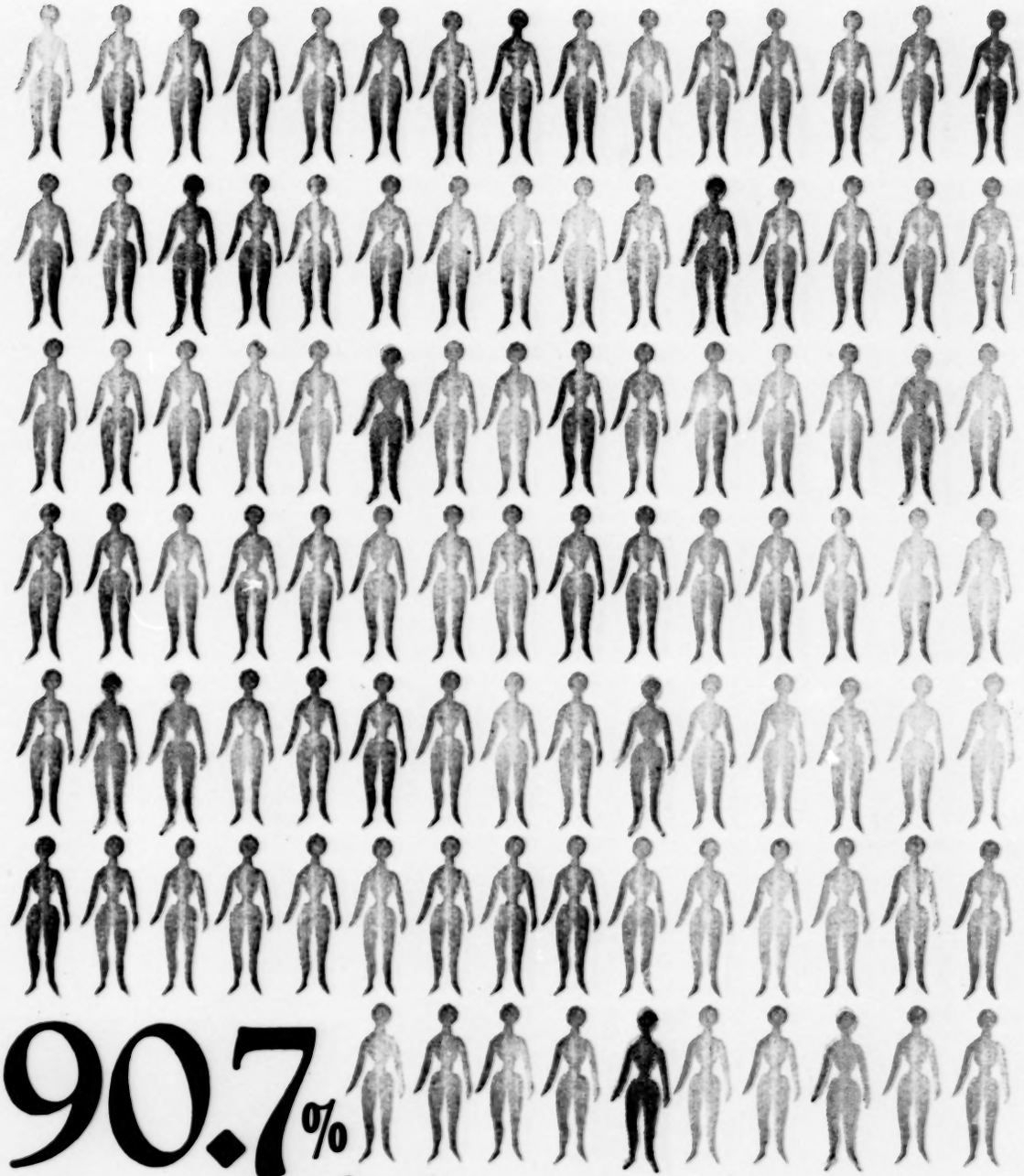
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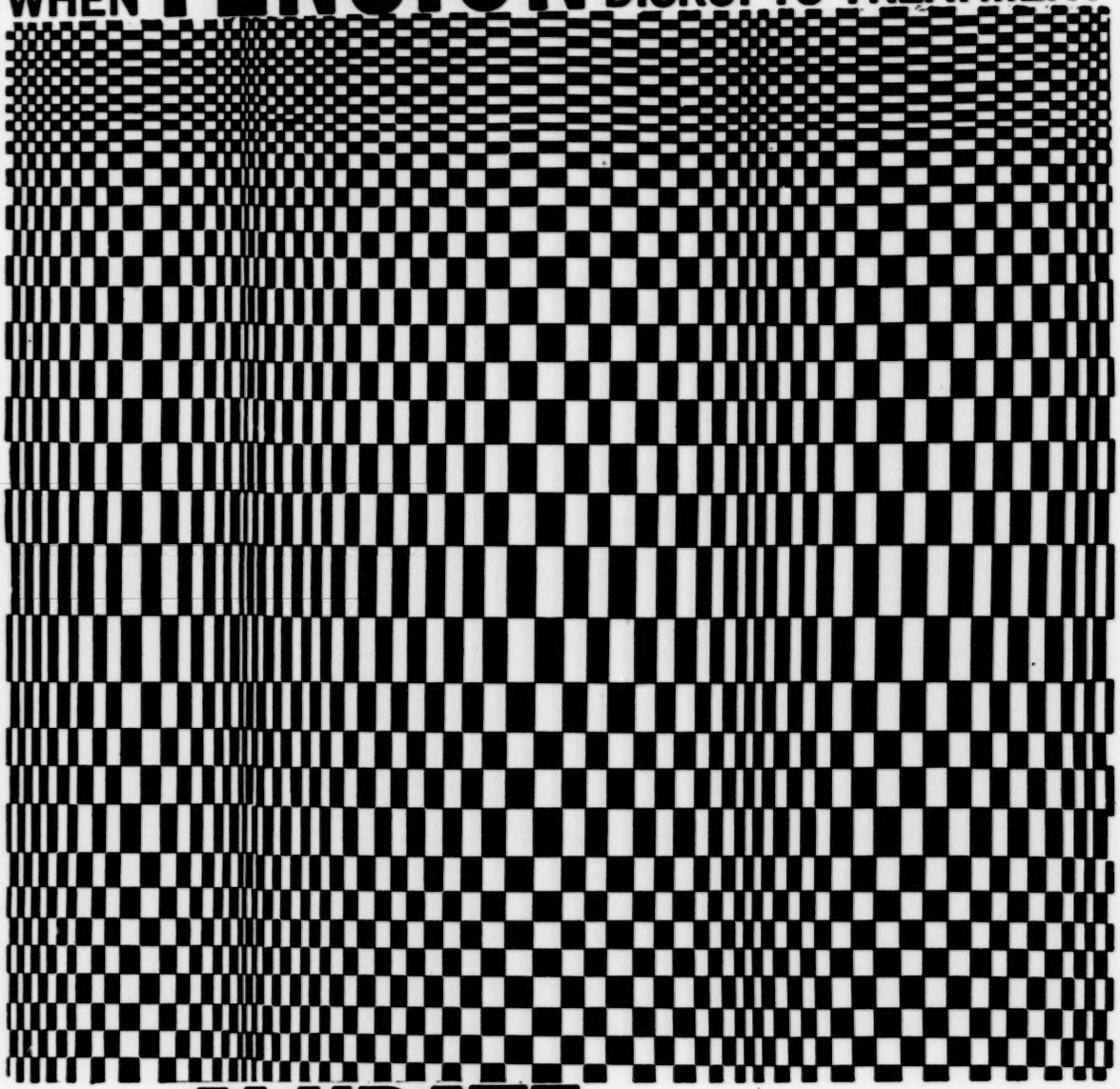
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*Murphy, H. S., *et al.*, Scientific Exhibit, A.M.A., Dec. 1-4, 1950, Dallas, Texas

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Knauff, R. E.; Fajans, S. S.; Ramirez, E., and Conn, J. W.:
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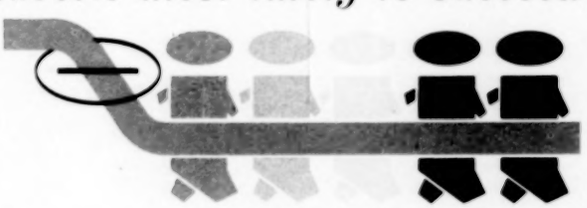
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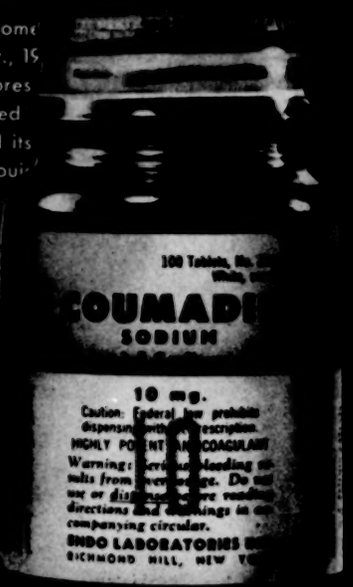
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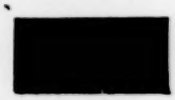
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AVERAGE DOSE

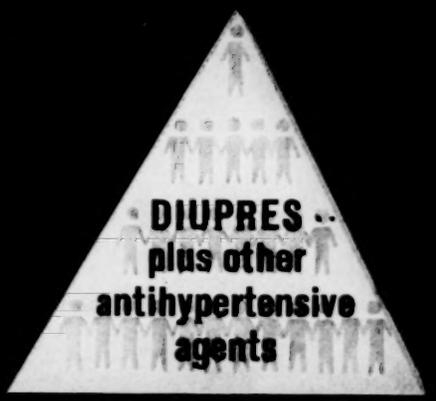
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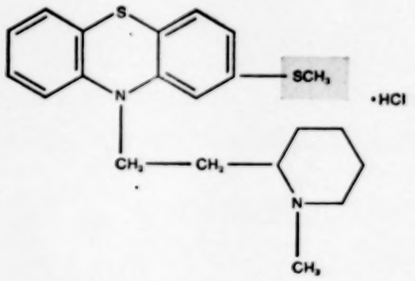


greater specificity
of tranquilizing action
—divorced from such
"diffuse" effects as
anti-emetic action
—explains why

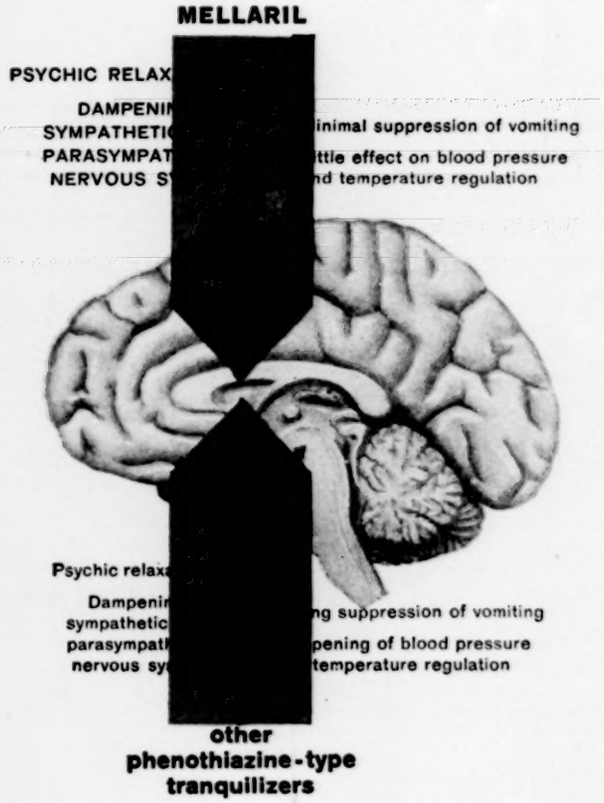
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SEVERE—in agitated psychotic states as schizophrenia, manic depressive, toxic psychoses, etc.:		
Ambulatory	100 mg. t.i.d.	200-400 mg.
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*Ostfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959.

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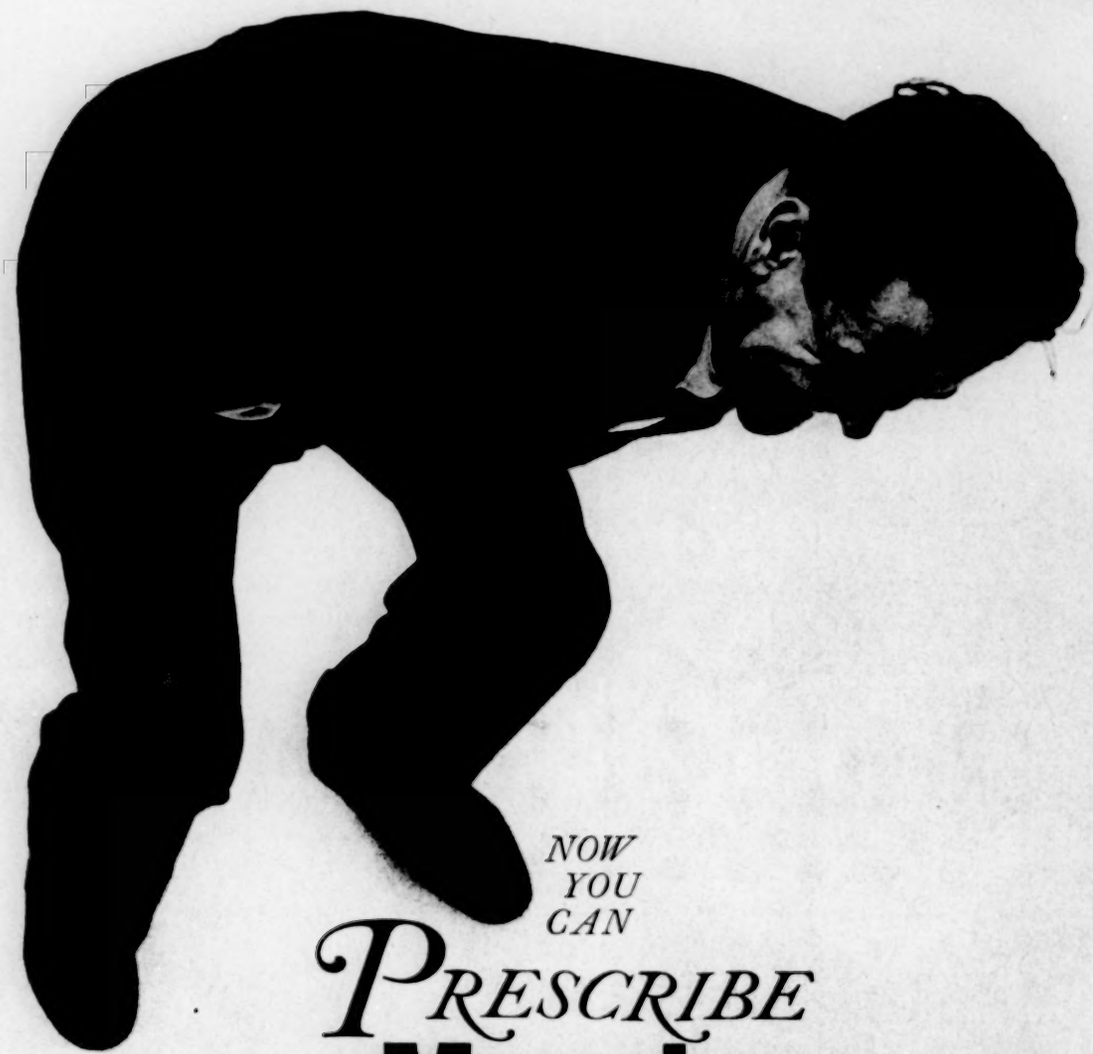
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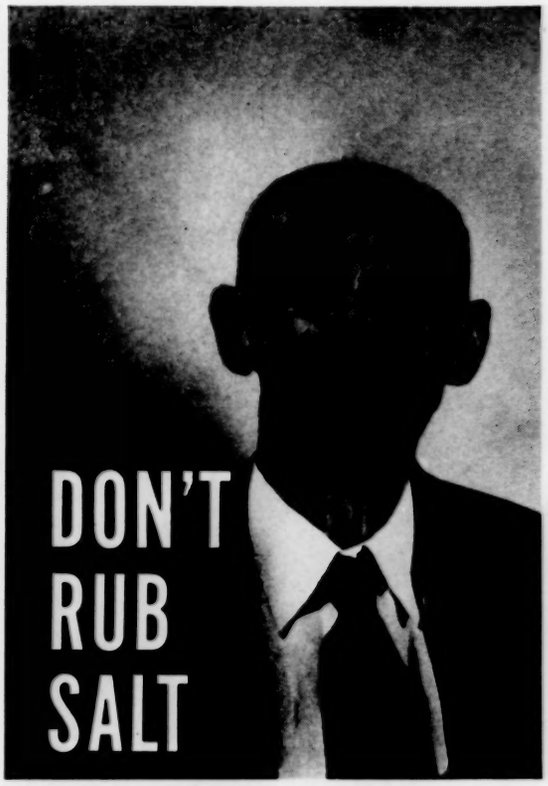
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1. Peiser, U.: Med. Klin. 50:1479 (Sept. 2) 1955. 2. Berndt, R.: Arzneimittel-Forsch. 5:711 (Dec.) 1955. 3. Rostalski, M.: Zentralbl. Gynäk. 78:1153 (July 21) 1956. 4. Holbrook, A. A.: Am. Pract. & Digest Treat. 10:842 (May) 1959.

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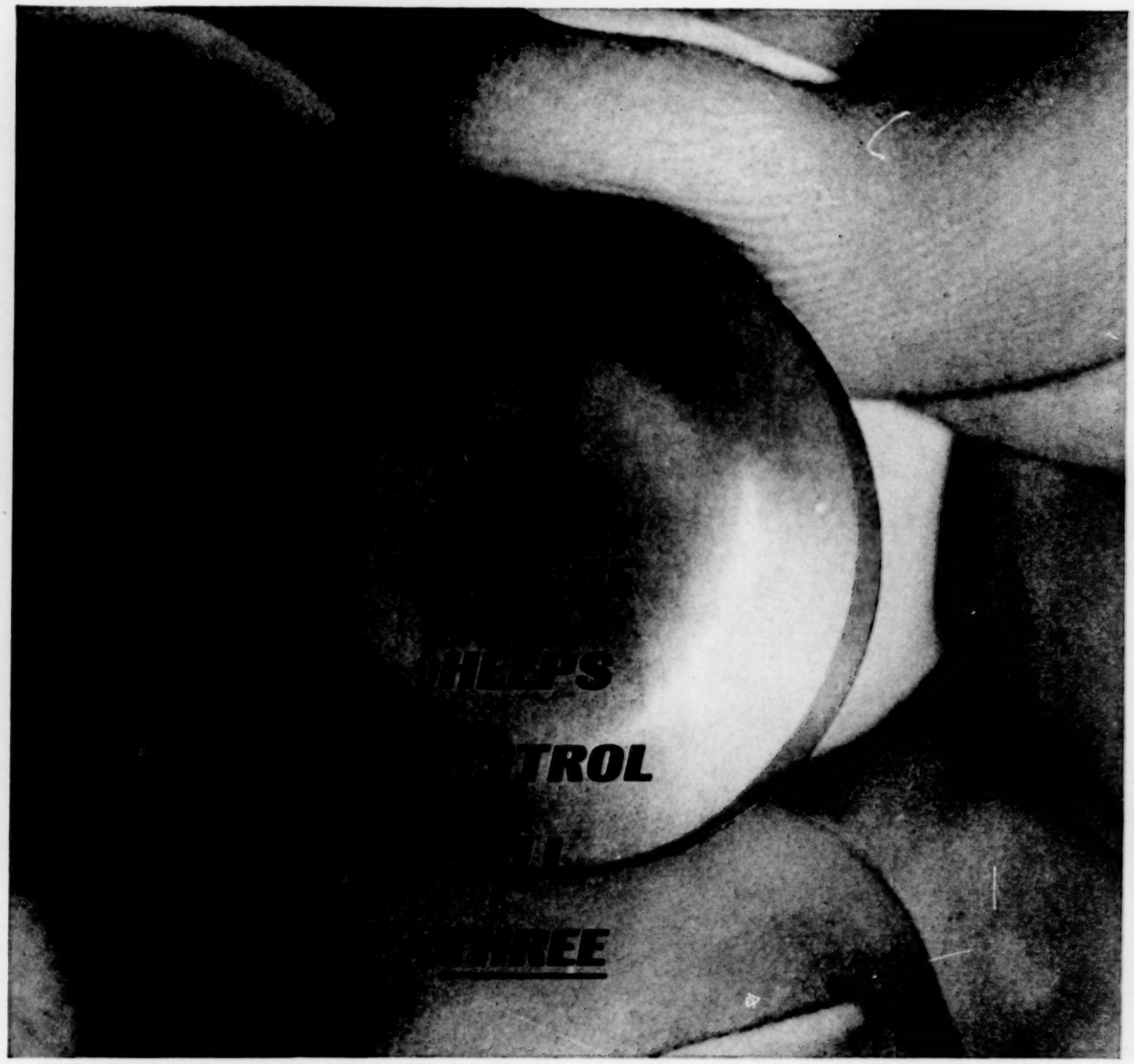
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antiemetic
antinauseant

no sedative properties
no tranquilizer side effects

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Calcium pantothenate	10 mg.	¼ lb. of fried beef liver
Ascorbic acid (Vitamin C)	**250 mg.**	¾ lb. of cooked broccoli

*These common foods are among the richest sources of B vitamins and ascorbic acid. H. A. Wooster, Jr., Nutritional Data, 2nd Ed., Pittsburgh, 1954.

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Glyceryl guaiacolate ..... 100 mg.



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(exempt narcotic)



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Glyceryl guaiacolate ..... 100 mg.
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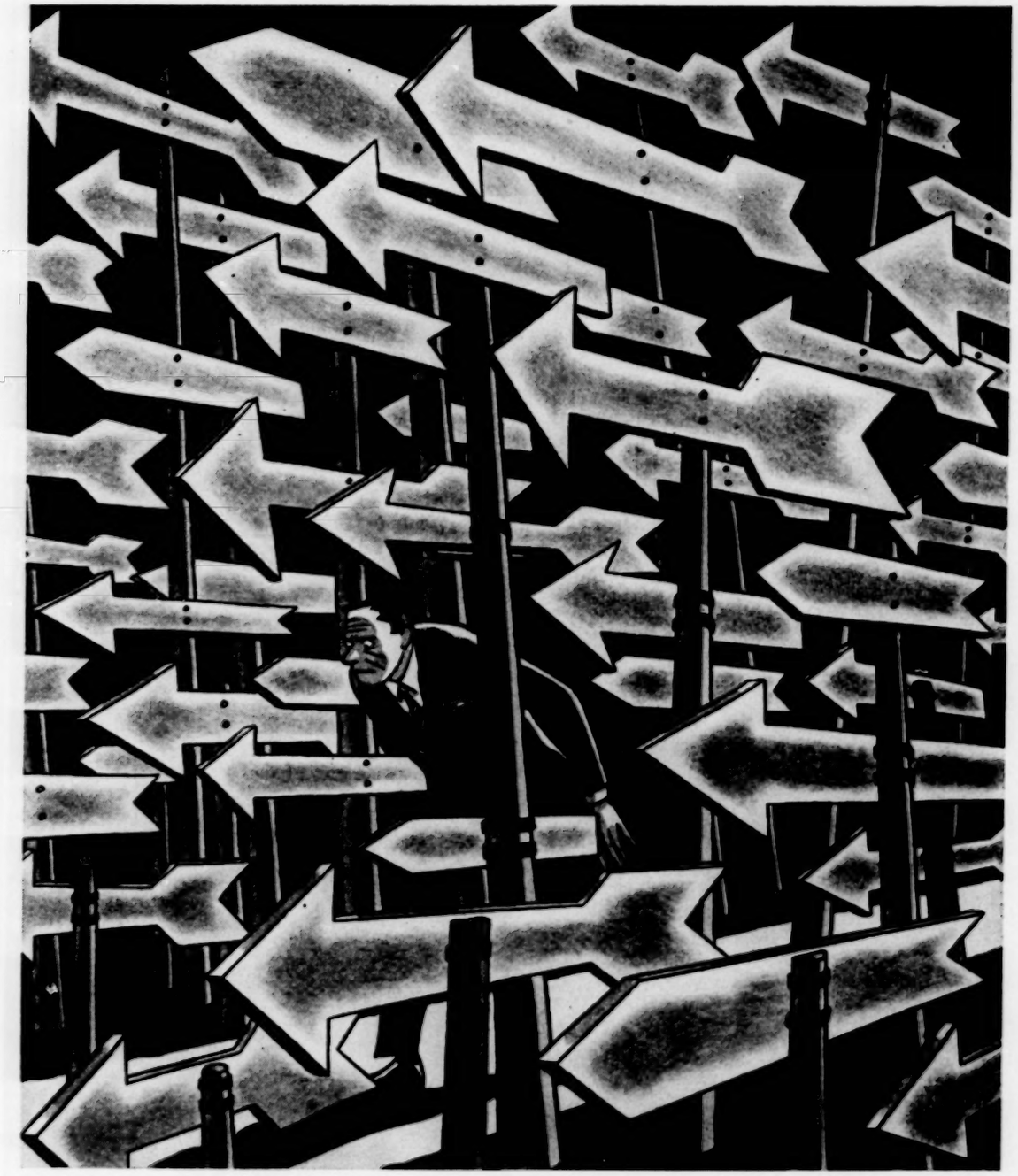
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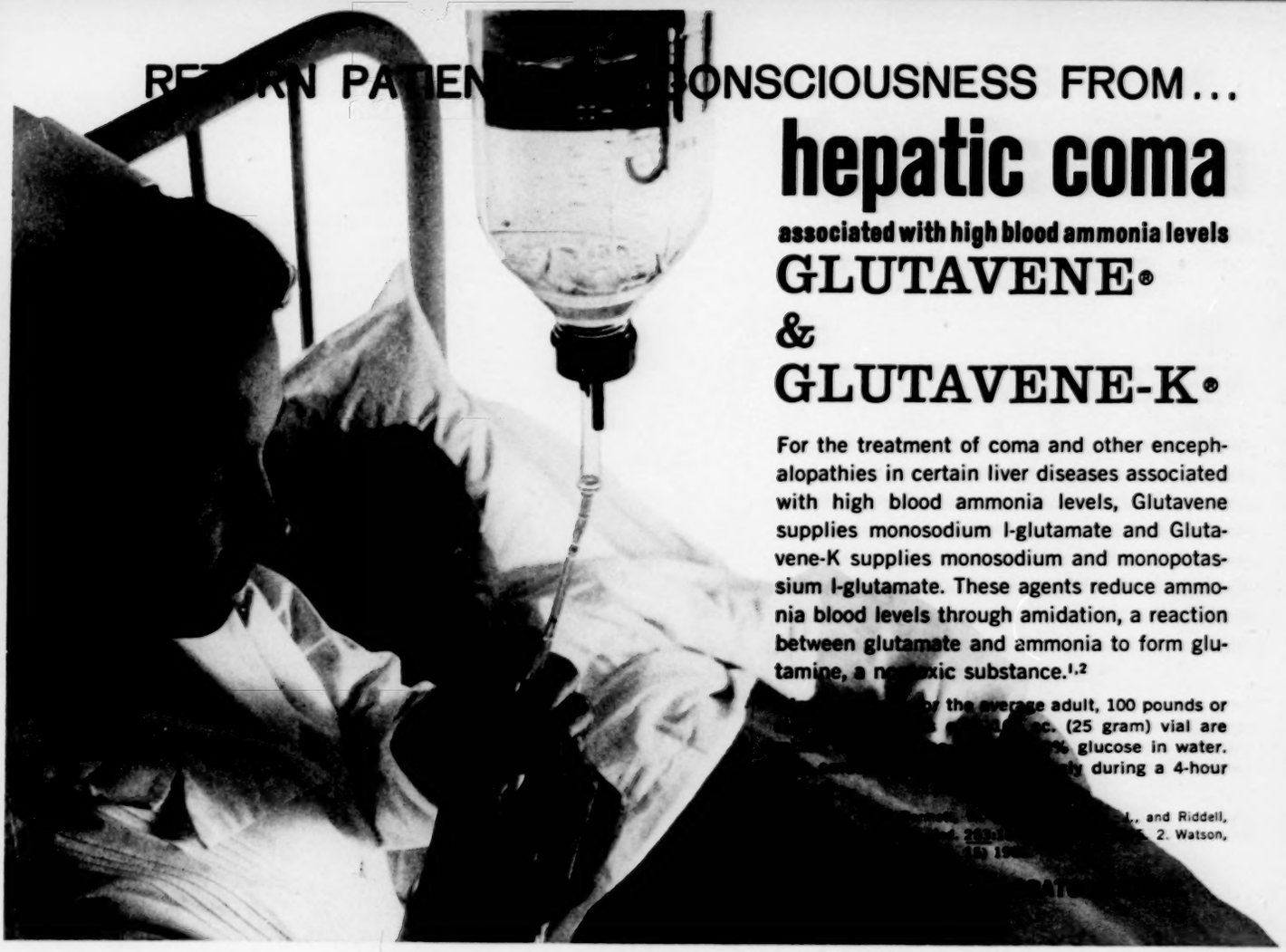
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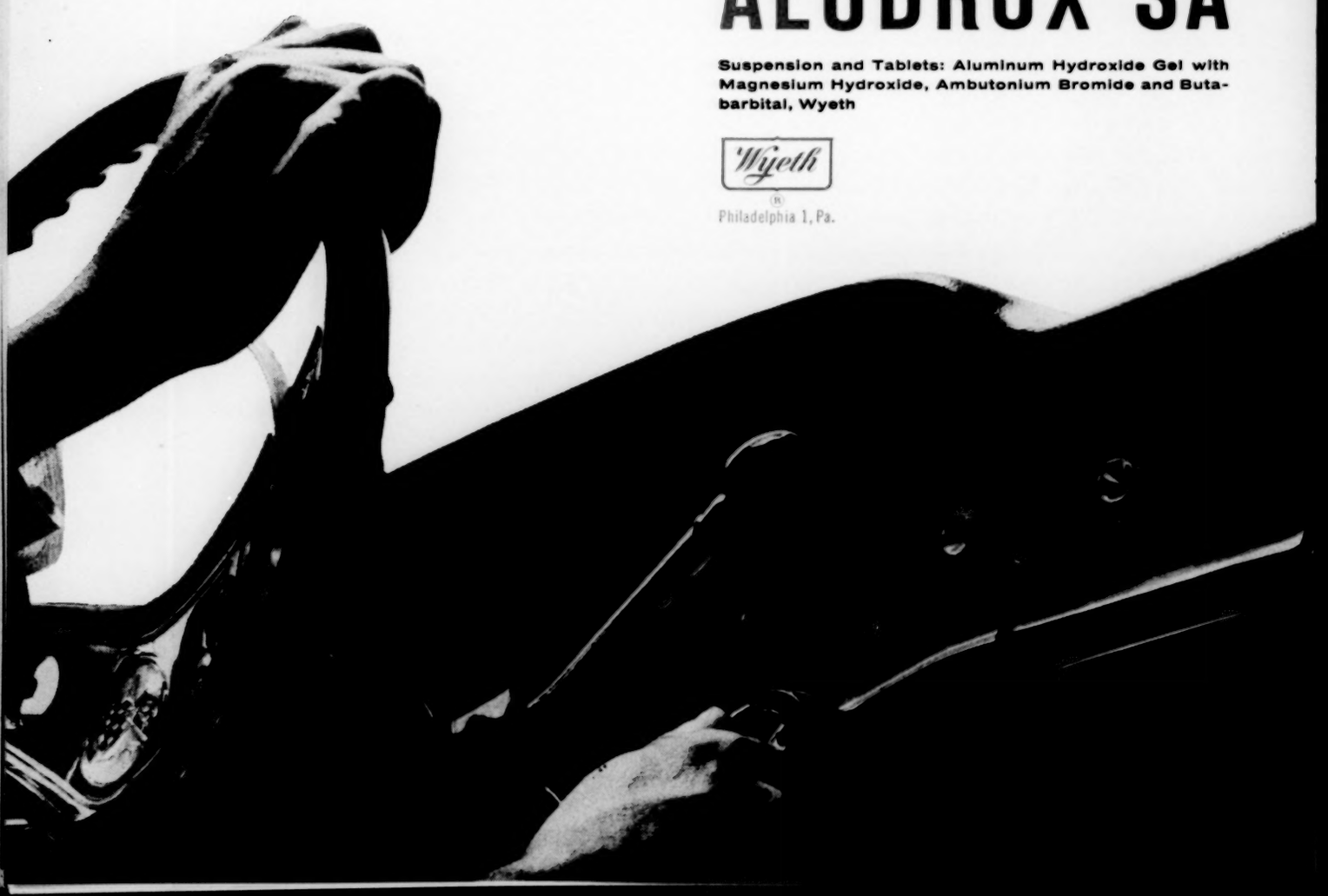
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Prigot, A.; Felix, A. J., and Mullins, S.: Paper presented at the Symposium on Antibacterial Therapy, Michigan and Wayne County Academies of General Practice, Detroit, September 12, 1959 (published Nov. 1959)

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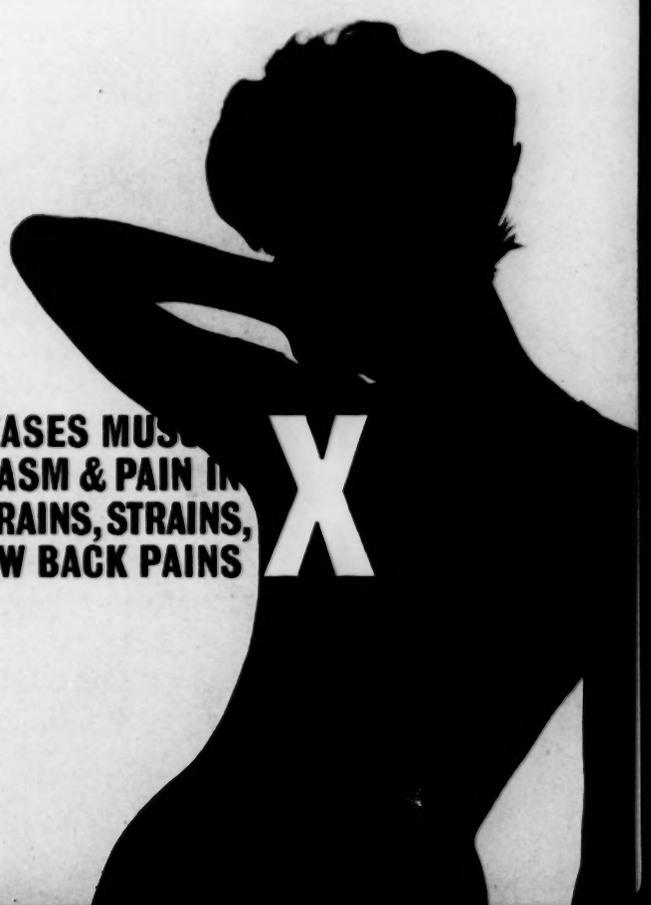
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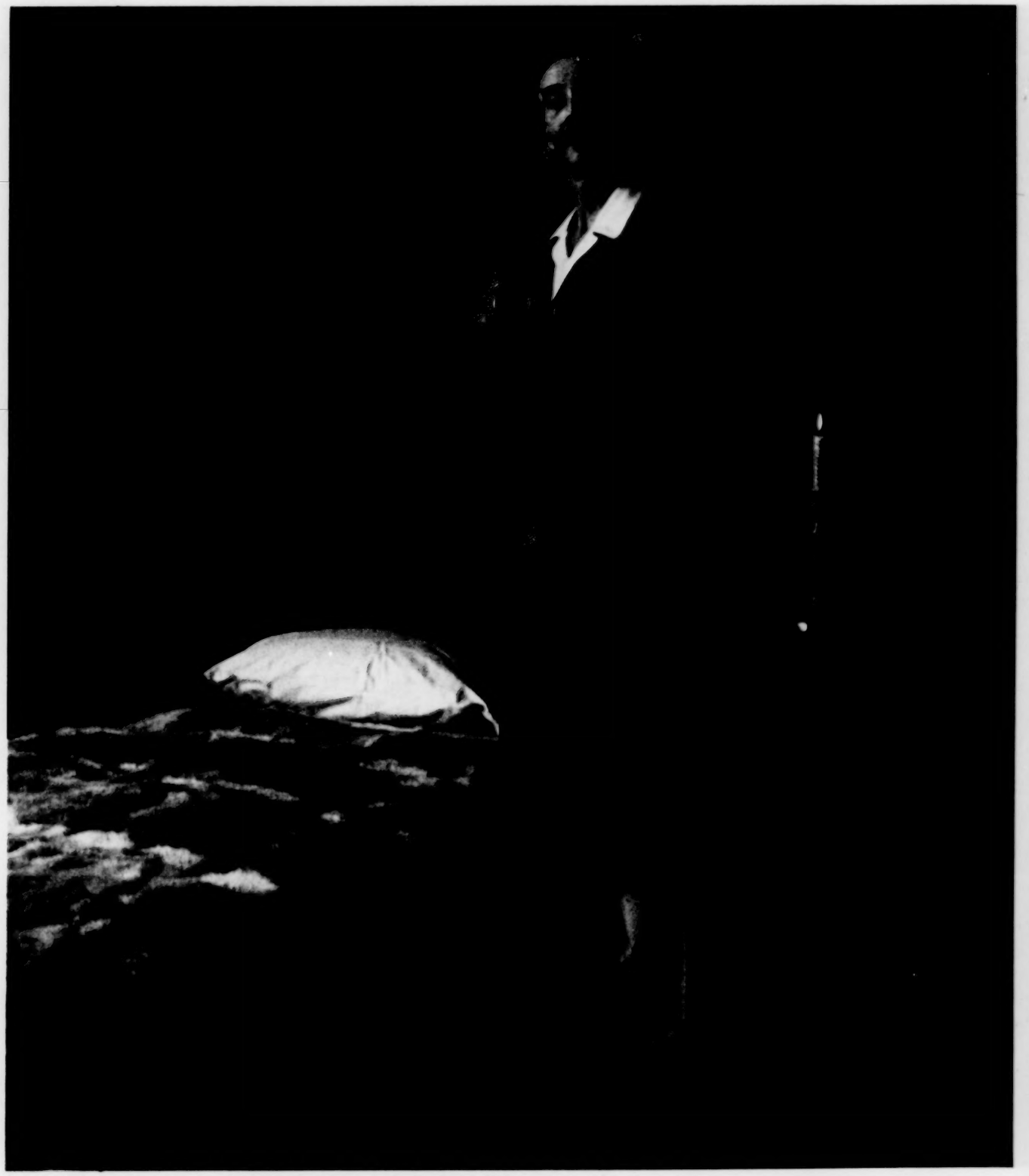
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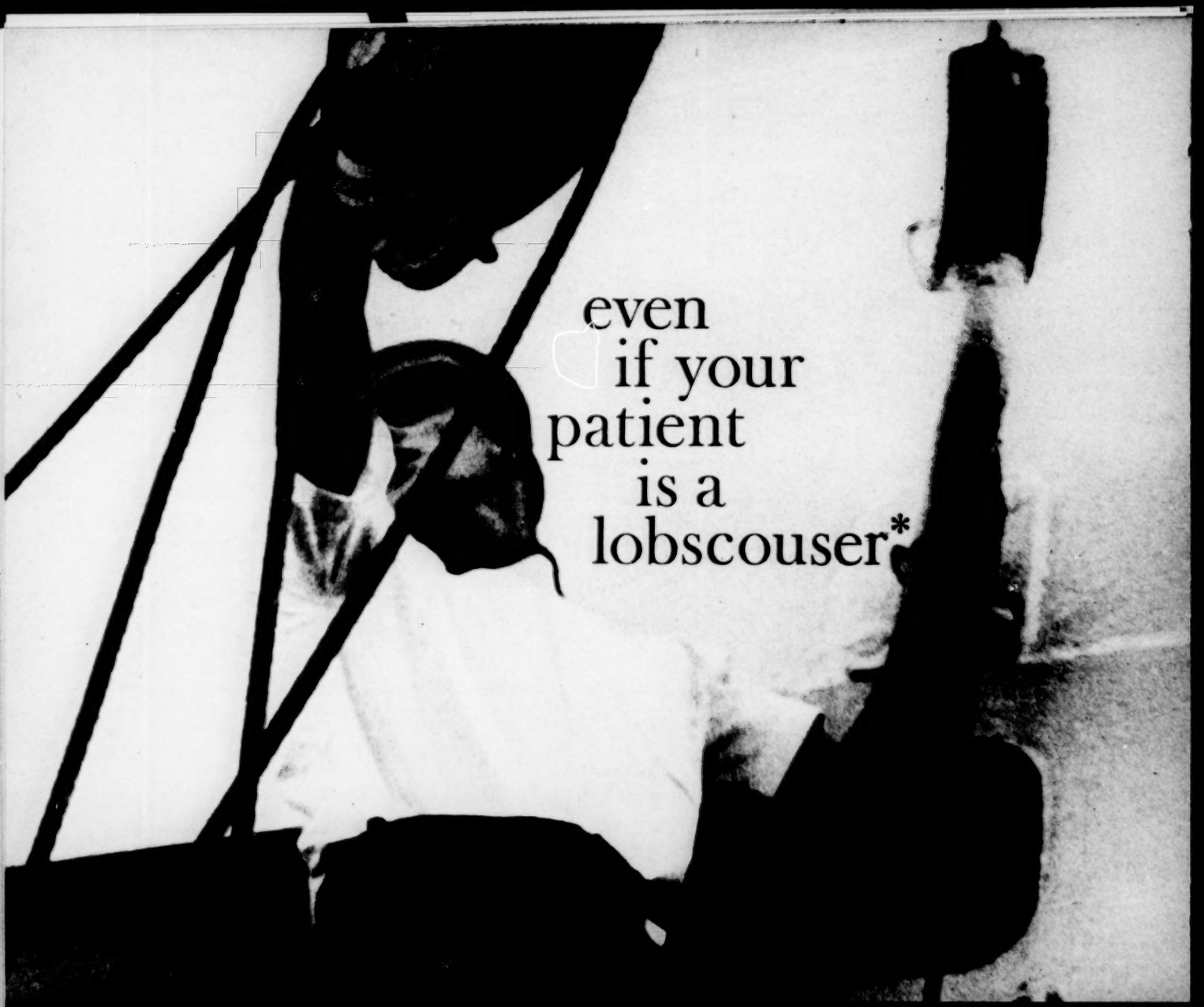
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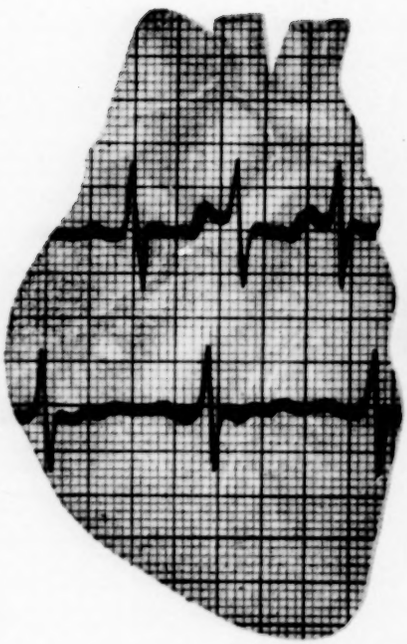
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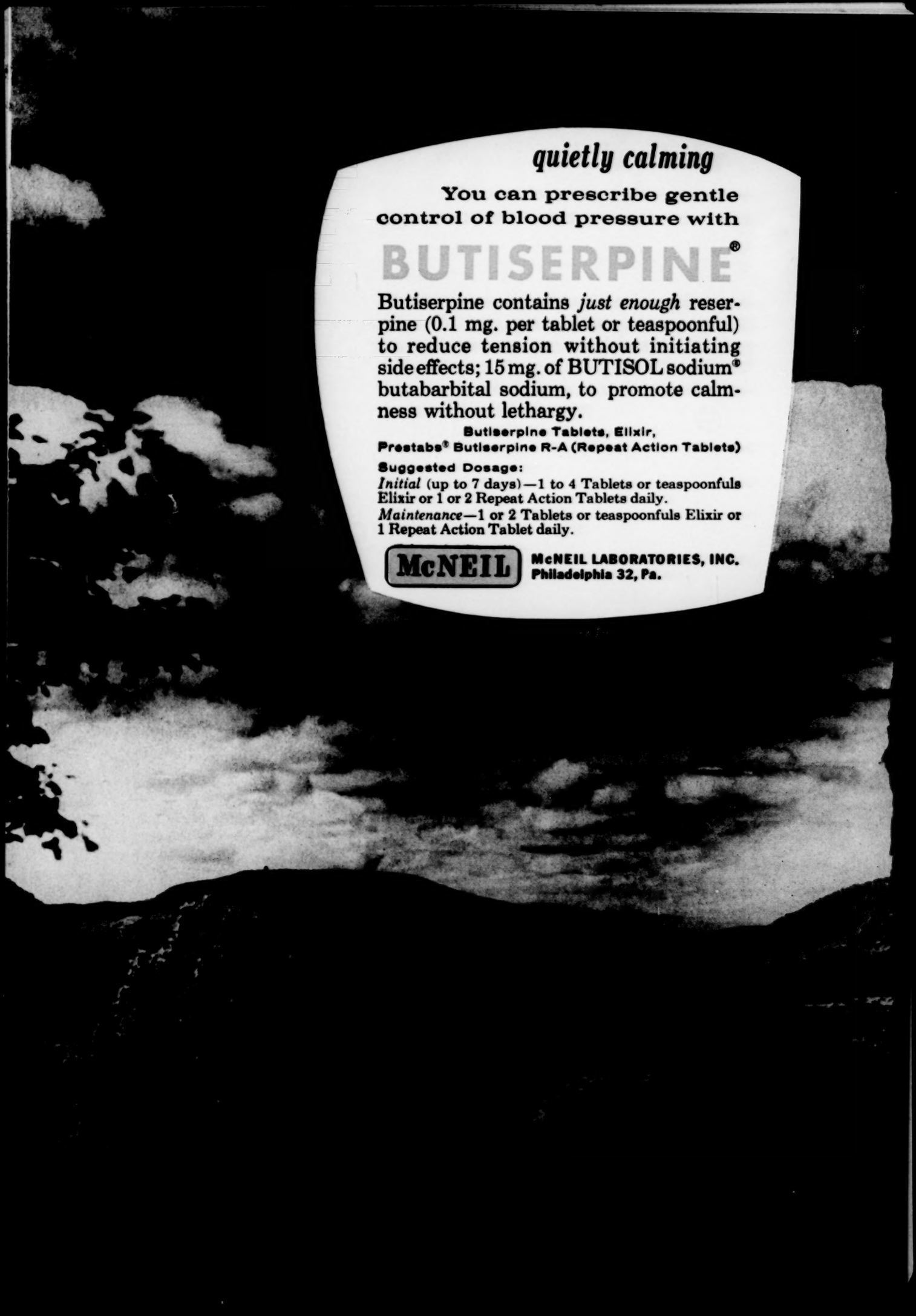
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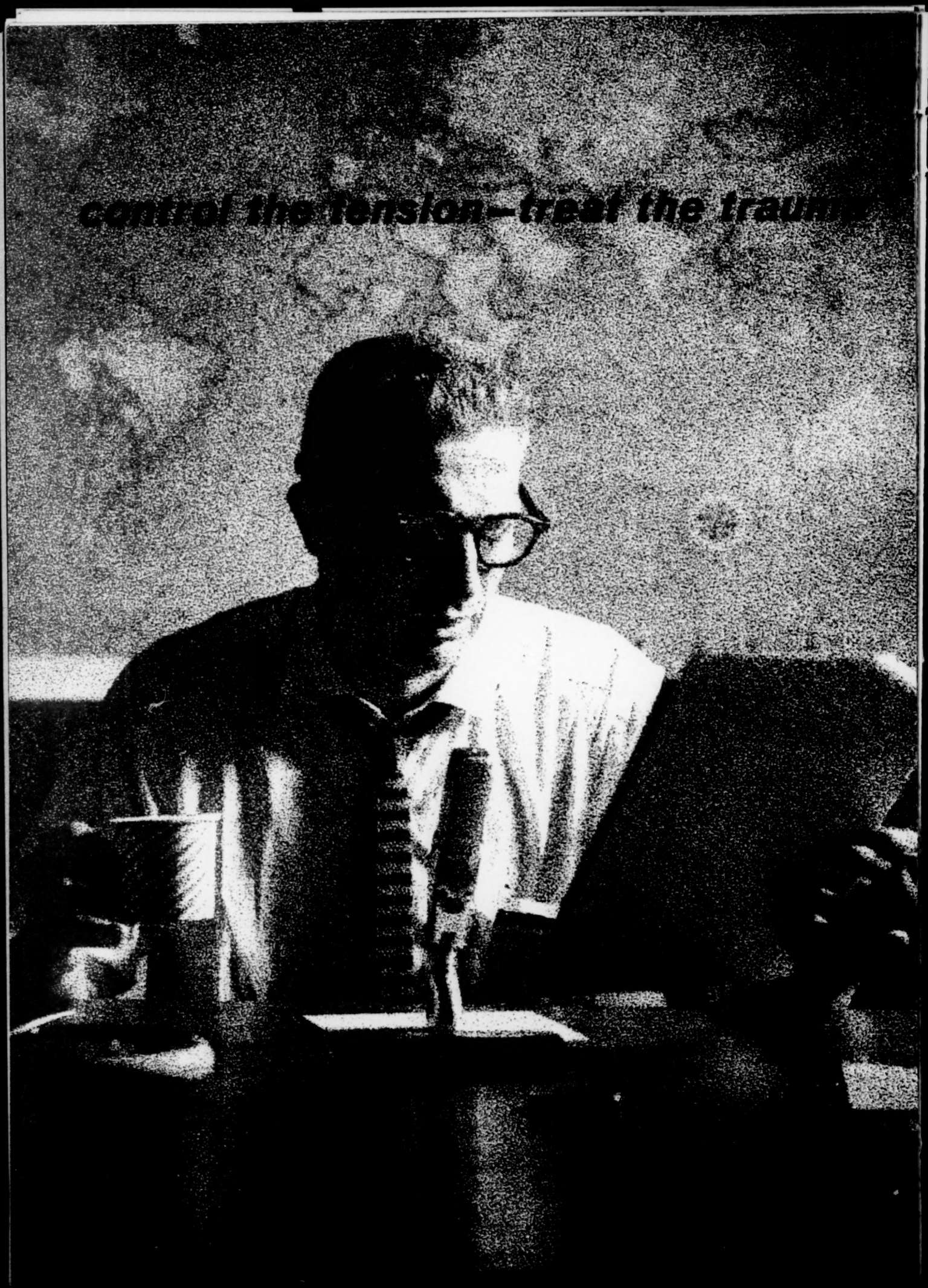
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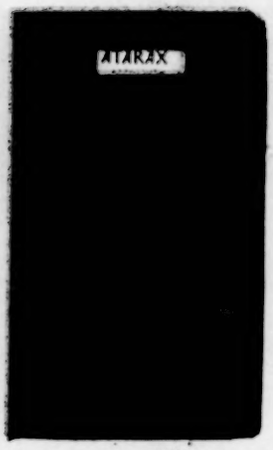
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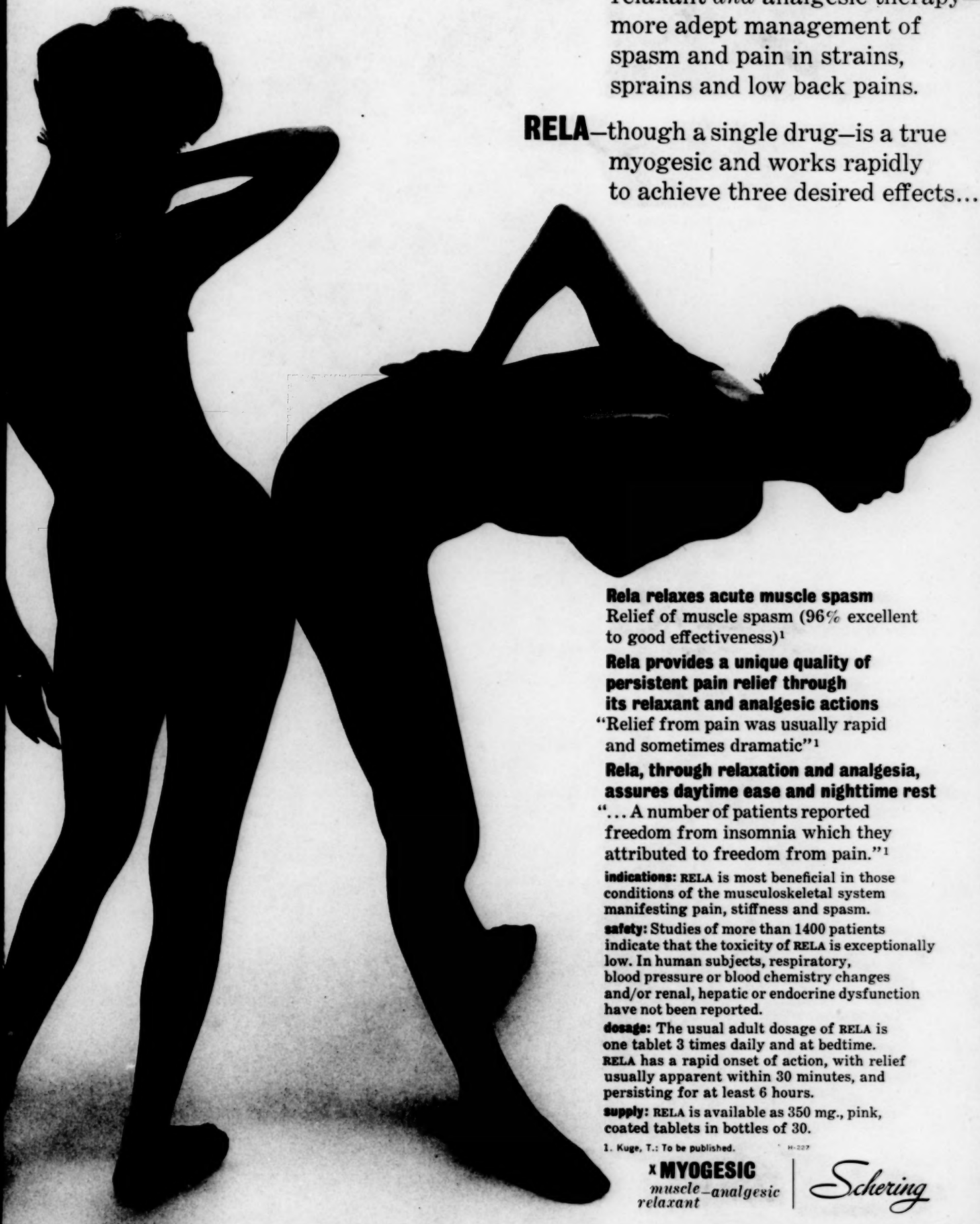
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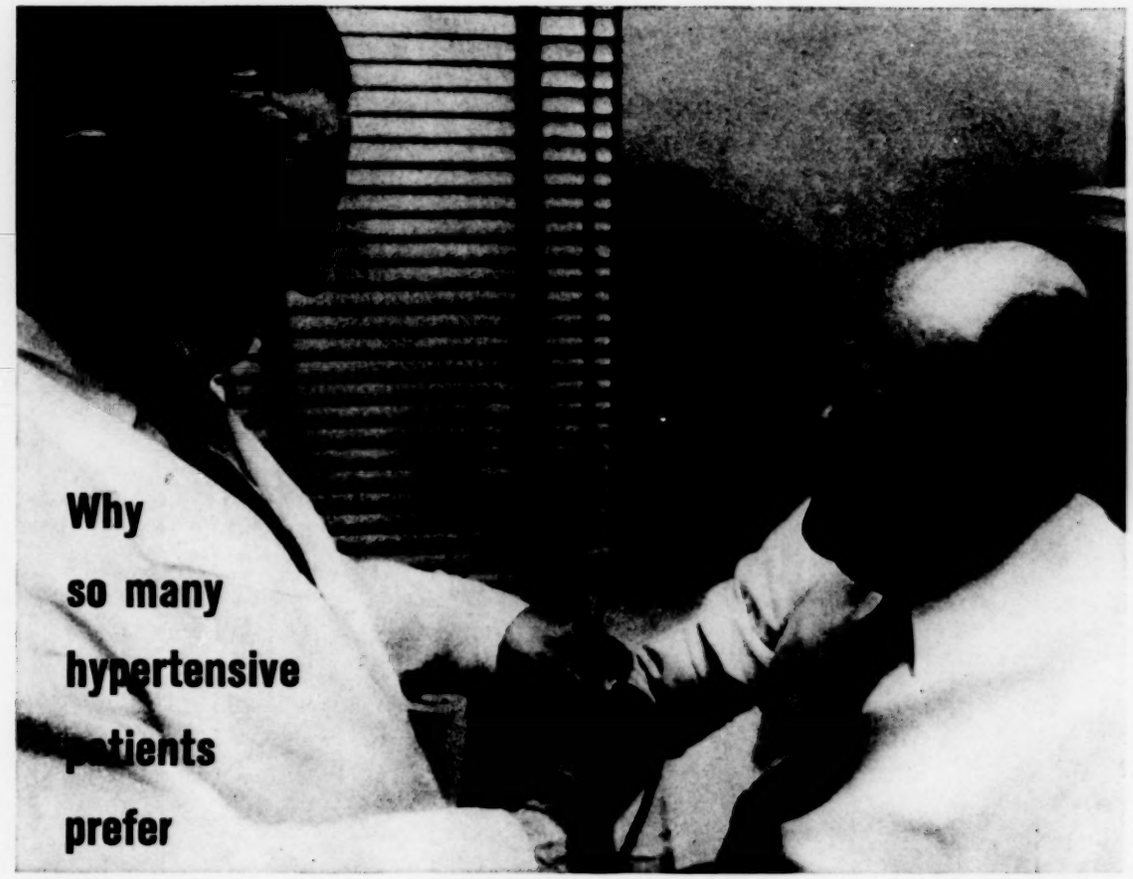
Krantz, J. C., Jr.: The restless patient—A psychologic and pharmacologic viewpoint. Current M. Digest 25:68, Feb. 1958.

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The American Journal of Medicine

VOL. XXVIII JANUARY, 1960 NO. 1

Editorial

The Kidney in Health; The Nephron in Disease

ANY formulation of the pathophysiology of chronic renal failure must begin with the basic question: Is urine formed from residual healthy nephrons or diseased ones? Both views have had their supporters over the years and perhaps, as we intend to put forward, both have suffered from the all too encompassing generalization.

The inherent difficulties in unraveling this dilemma are formidable. With the formation of urine taking place in a heterogeneous nephron population of greater than 2 million units, data derived by the clearance method must of necessity represent a crude composite view. Secondly, our acquisition of knowledge of normal renal physiology has been painfully slow because of the complexities of a system utilizing filtration, reabsorption and secretion acting together in a dynamic equilibrium to produce the urine as an end product. Thirdly, before the advent of biopsy material, functional anatomic correlation was largely reconstructed from end-stage postmortem specimens. And lastly, the bizarre and diversified structural alterations of the nephron population in disease cast further suspicion on the validity of clearance data. This is especially true of clearance ratios, which represent an even greater degree of abstraction. Oliver, culminating his work [on the microdissection of diseased kidneys and in the classic paper "When is the Kidney not a Kidney?" [*1*], eloquently expresses the skeptic's view. "The kidney no longer exists as a meaningful structural or functional concept—there remains only a heterogeneous collection of various and disparate organs, the abnormal nephrons of chronic renal disease." In view of recently obtained knowledge regarding function of the normal and diseased kidney, our concept of the pathophysiology of chronic renal failure must be re-examined.

The conventional view, held for many years, has maintained that disease alters specific tubular sites for reabsorption and secretion of various substances and for the concentration and dilution of urine. Thus urine formed from diseased kidneys was characteristically thought to be formed from diseased nephrons.

During the recent past an alternative view has been put forward by several groups [*2–7*]. This newer concept shifts emphasis away from qualitatively diseased tubular sites by suggesting that the majority of damaged nephrons do not contribute to the formation of urine. Instead, there is a quantitative reduction in nephrons with normal remaining units now exposed to a greater obligatory solute load. Each functioning nephron is visualized as being exposed to an osmotic diuresis which results in polyuria, sodium wasting and inability to effect maximal concentration or dilution of the urine. Experimental evidence for this concept was first obtained in 1899 by Bradford [*8*] when he demonstrated that progressive surgical reduction of renal mass in dogs produced uremia and large quantities of dilute urine. Hayman [*2*] in 1933 and Platt [*3*] in 1950, working with the dog and the rat respectively, confirmed the

appearance of isosthenuria after subtotal nephrectomy. Support for the production of "normal" urine in chronic renal failure also has accumulated. The absence of glycosuria in the majority of patients with chronic renal disease is a well established clinical observation. Nickel et al. [9] have shown that some patients with uremia can conserve sodium efficiently when given a low sodium intake. The ability to obtain exceedingly dilute urine in patients with uremia by progressive daily increments in fluid intake has been shown by Guild et al. [10]. Similarly, diluting capacities expressed as free water clearance per unit of glomerular filtration rate (C_{H_2O}/GFR) have been found to be normal in dogs and man [11] during varying stages of renal failure. Concentrating capacity expressed as free water reabsorption per unit of glomerular filtration rate ($T^c_{H_2O}$/GFR) was normal in human subjects [12] with glomerular filtration rates above 60 cc./minute. More recently Bricker et al. [7,13–14] have produced unilateral glomerulonephritis and pyelonephritis in dogs. Simultaneous studies of the diseased and the normal kidneys revealed essentially identical values on both sides for p-aminohippurate secretion (Tm_{PAH}), glucose reabsorption (Tm_G) and phosphate reabsorption (Tm_{PO_4}), when their values were expressed per unit of glomerular filtrate. Free water reabsorption ($T^c_{H_2O}$) and free water clearance (C_{H_2O}) per unit of glomerular filtrate on the diseased side closely parallel those of the normal kidney (although maximum urine concentration was impaired in the diseased kidney). And, the finding of normal glucose titration curves with equal splay for normal and diseased kidneys [14] would imply no increase in the heterogeneity of the remaining nephron population in renal disease.

In view of these findings Oliver's observations could be interpreted as indicating that the most bizarre nephrons do not contribute significantly to the formation of urine. The decreased flexibility in maintaining homeostasis during sodium, potassium, acid or water loading which characterizes renal insufficiency could therefore be a reflection of a diminished filtering surface area and tubular mass. This reduced nephron population functions normally but is exposed to a relative increase in both solute and water load.

Attractive as this newer concept of renal failure may appear, there is evidence suggesting that impaired tubular function (the conventional view) also plays a role in the formation of urine in certain kinds of chronic renal disease. Moreover, compensatory hypertrophy of nephrons, uninvolved by disease, may modify renal function. The evidence in favor of these influences will now be presented.

First to be considered is the role of hypertrophy in chronic renal failure. That the kidney possesses a striking capacity for hypertrophy in size and function has been well documented in the earlier literature [15–17]. The microdissection studies of Oliver [1,18] show this hypertrophy to consist of an enlargement in the caliber of renal vessels, an increase in size of the glomeruli, and an enlargement of tubular structure. The proximal convoluted tubule is chiefly affected, increasing up to eight times in length and four times in diameter, so that proximal tubular volume increases by some twentyfold. Nephron units accomplish this feat by a process of both cellular hypertrophy and hyperplasia. How hypertrophy is mediated remains unclear, but it can be brought about by surgical resection, clinical and experimental renal disease, and by protein and, to a lesser extent, urea loading [19–20]. However, Block et al. [21] have shown that after unilateral ureteroduodenostomy the contralateral kidney fails to hypertrophy to the extent that it does with unilateral nephrectomy. This suggests that other factors besides solute load are important. Certain endocrine renotrophic effects have been implicated. Thyroidectomy and, to a greater extent, hypophysectomy greatly limit hypertrophy after unilateral nephrectomy [22–24]. The process of hypertrophy can be set in motion in as short a period as twenty-four hours following nephrectomy in rats, as evidenced by the appearance of increased mitosis [25]. After nephrectomy in man, increased functional improvement has been observed within a week [26] and may continue for several months or longer [27]. Finally, the hypertrophy following surgical removal of tissue appears to be morphologically identical with that of the spared nephron units in varying stages of chronic renal disease.

What are the implications of these drastic changes in renal architecture? Following unilateral nephrectomy in both dog and man, renal function ultimately improves to approximately 75 per cent of the values before nephrectomy [2,27,28]. Since no new nephrons are formed

and evidence does not support intermittency of function in normal mammalian kidneys, each nephron must increase blood flow and glomerular filtration by some 50 per cent. Thus the kidney compensates for a decreased number of nephrons by more efficient perfusion of remaining hypertrophied units. The clinical observation that blood urea nitrogen (BUN) rises very late in renal disease may be attributable not only to the geometric nature of the curve relating BUN to GFR [*29*] but also to the fact that hypertrophy would tend to delay and minimize the reduction in urea, creatinine and inulin clearances. Hence renal disease would be further submerged below the level of clinical detection. It can be estimated from experiments in both animals and man after nephrectomy that abnormally low inulin clearances are first detectable with a reduction in nephrons of 30 per cent or greater. On a normal protein diet BUN becomes detectably elevated after a 75 per cent reduction, and symptoms of uremia do not appear until the nephron population has been reduced to approximately 10 per cent.

Another important consequence of hypertrophy concerns tubular function. There is good evidence to indicate that transport per functioning nephron is more efficient both by virtue of cellular hyperplasia and increased transport capacity in each tubular cell. A bit of "nephron arithmetic" indicates that if GFR per nephron is increased by 50 per cent after unilateral nephrectomy, reabsorptive capacity must increase by a similar amount to prevent a drastic glomerular-tubular imbalance. Cellular anatomic hypertrophy must be translatable into transport hypertrophy. An excellent illustration of this important concept can be found in an experiment by Kolberg [*30*]. Mudge and Taggart [*31*] had shown that sodium acetate infusion could almost double the Tm_{PAH} in dogs, presumably by stimulation of aerobic metabolism after conversion to active acetate. This experiment was repeated by Kolberg and then, after waiting a suitable time for development of hypertrophy following unilateral nephrectomy, Tm_{PAH} was again determined before and after acetate infusion. Tm_{PAH} values in one kidney were slightly less than they were before nephrectomy in two kidneys but now acetate infusion had a negligible effect in further increasing Tm_{PAH}. Thus the process of hypertrophy represents a utilization of reserve capacity to increase active transport, and once achieved, a further increase in transport following stress is no longer demonstrable.

If functional as well as anatomic hypertrophy accompanies renal failure, this could account for maintenance of a relatively normal body electrolyte composition until late in disease; then further stress, represented by an exogenous load of potassium or hydrogen ions, could produce acute decompensation. The studies of Schwartz et al. [*32*] indicate that near maximum hydrogen secretion per nephron is maintained in chronic renal disease. When uremic subjects with lowered plasma bicarbonate concentrations were given a single dose of ammonium chloride or hydrochloric acid, titratable acidity and ammonium excretion were only minimally increased. Several investigators have shown that potassium clearances may exceed those of inulin two- to threefold in the face of renal failure [*33–35*]. This may very well represent increased secretion of potassium through distal tubular sites; excretion of a larger percentage of filtered potassium also may play a role. Hence another factor in the inflexibility of renal function in disease is the compensatory increase in the transport capacity per functioning renal tubular cell, which then has a more limited capacity to respond to any further stress.

The second modification in the concept of chronic renal failure is the role of intrinsic damage to tubular function and renal architecture. Evidence for the formation of inherently normal urine from diseased kidneys has already been presented, but are we to neglect the differences in the various types of pathologic change which produce chronic renal insufficiency? If we have reason to doubt the importance of the various bizarre and distorted fragments of diseased nephrons described by Oliver must we not still consider what Homer Smith [*36*] classified as the "impotent nephron" (normal or supranormal filtration through a damaged tubule)? The studies of Michie and Michie [*37*] on unilateral pyelonephritis in man and of Bricker et al. [*7*] on experimental unilateral pyelonephritis in dogs stress the consistency of the GFR/Tm_{PAH} ratios in all stages of disease. However, Earle's [*38*] and Raaschou's [*39*] studies show an increased GFR/Tm_{PAH} ratio for all but the early stages of pyelonephritis. The basic criticism in the interpretation of clearance ratios in renal disease has been mentioned. Since only a small deviation in glomerular-tubular balance can produce profound effects on urine

composition such gross methods of analysis are open to suspicion.

Chronic glomerulonephritis, hypertensive renal disease and diabetic glomerulosclerosis primarily involve the blood supply to glomeruli, with resultant damage to tubules. Here the concept of destruction of entire nephron units appears plausible. However, hydronephrosis and polycystic disease produce obstructive, ballooning tubular lesions. In polycystic disease these "incompetent nephrons" have been shown by direct puncture to retain some function [*76*]. Pyelonephritis appears to advance interstitially, the medullary region being inherently more susceptible to early bacterial invasion [*40–43*]. Might not impotent nephrons play a role in the formation of urine in these latter conditions? The situation is made more complex and difficult to interpret because of possible hypertension, congestive failure and pyelonephritis complicating any type of primary chronic renal disease. Since the pathologist cannot determine whether the impotent nephron contributes to the formation of urine, the issue must be decided on the basis of clinical evidence.

Although, as previously stated, there is sound evidence that exogenous osmotic load can limit final urine concentration, clinical evidence suggests that various types of renal disease result in early loss of concentrating ability with little or no nitrogen retention. Raaschou [*39*] showed this in a series of patients with pyelonephritis. Brod [*44*] compared maximum urine specific gravities in a large series of patients with pyelonephritis, glomerulonephritis and hypertensive renal disease and found that at any comparable GFR the renal concentrating capacity was most significantly lowered in the group with pyelonephritis. Recently Winberg [*45*] has shown a significant reduction in maximum urine osmolarity in children with acute pyelonephritis without azotemia. In addition, early marked loss of concentrating ability has been observed in both hydronephrosis and polycystic renal disease [*2,46*]. Finally, the passage of urine with a maximum specific gravity below 1.010 in both pyelonephritis and polycystic disease has been noted by several investigators [*47,49*].

In view of recent knowledge regarding the production of hypertonic urine by means of a medullary countercurrent multiplying system [*50,51*], early concentrating defects correlate best with structural alteration in the medullary architecture and tubular integrity. Final urine concentration is dependent not only on solute load but also on tubular function and the composition of medullary interstitial fluid [*52,53*]. On this basis, the loss of urine concentrating ability out of proportion to diminished glomerular filtration in recovery from acute tubular necrosis [*12*], and hypokalemic [*54*] and hypercalcemic [*55*] nephropathy could be due to either functional or structural impairment of cell function.

Unlike the experimental animal [*13,14*] and the human subject with slight impairment of filtration rate [*12*], patients with more advanced renal disease have depression of free water reabsorption ($T^c_{H_2O}$) out of proportion to decrease in filtration rate. In these persons with renal failure the ratio $T^c_{H_2O}$/GFR was consistently below that found in normal subjects [*77*]. The early concentrating defects, already mentioned, in hydronephrosis, polycystic disease, and in many cases of pyelonephritis, correlate well with destruction of medullary architecture or tubular integrity. Consistent, marked decrease in concentrating ability is associated with bilaterally contracted kidneys, with distortion and contraction of the medullary architecture.* It may be concluded, therefore, that the isosthenuria of renal disease cannot be explained solely in terms of nitrogenous solute load. Specific functional or structural alterations in the concentrating mechanism also may be present.

Schwartz and Relman [*32,56*] have emphasized that the acidosis of renal insufficiency is tubular in origin, both in terms of an absolute reduction in hydrogen ion secretion and frequently in primary bicarbonate wasting. When the hydrogen-secreting mechanism is compromised by chronic renal disease, plasma bicarbonate concentration falls as a result of accumulated endogenous and exogenous hydrogen ions. If disease destroys total nephron units, diminished hydrogen secretion is accompanied by a corresponding reduction in filtration; therefore any fall in plasma bicarbonate con-

* The efficiency of the medullary countercurrent concentrating mechanism may very well be modified by: Differential destruction of the loop of Henle contained in juxtamedullary nephrons (only about one-seventh of the nephrons in the human kidney possess medullary loops of Henle); abnormal spatial configuration of both Henle's loop and vascular loops within the medulla with preservation of the maximum length of the long axis of these loops; washout of medullary interstitial osmotic gradients due to excessive blood flow to the remaining functioning nephron mass [*40*]; and possibly leakage into the interstitial space from damaged nephrons.

centration is roughly paralleled by rising levels of plasma phosphate, sulfate and organic anions. In primary renal tubular acidosis, a genetic defect in transport which limits hydrogen ion secretion and bicarbonate reabsorption, acidosis is associated with hyperchloremia. Similarly, when tubular failure predominates in chronic renal disease, hyperchloremic acidosis may be observed. Later in the disease process, hyperchloremia may disappear as filtration becomes grossly impaired. Since hyperchloremic acidosis in chronic renal disease is observed almost exclusively in hydronephrosis, polycystic disease and pyelonephritis with or without renal calculi or nephrocalcinosis [*46,57–59*], some degree of tubular damage predominates over the destruction of filtering surface. This represents further evidence for the existence of impotent nephrons in some types of chronic renal failure.

The finding of Bricker et al. [*60*] that unilateral nephritic dog kidneys conserved sodium as well as their normal counterparts when subjected to urea loads suggests that sodium wasting (as seen clinically) represents a tubular defect. Of the more than twenty cases of "salt losing nephritis" which have appeared in the literature since 1944, the majority have occurred in patients with pyelonephritis [*61–74*]. In a review of the records of a large number of patients with chronic renal failure, it was found that salt wasting was confined almost entirely to patients with polycystic disease, hydronephrosis and pyelonephritis [*46*]. In addition, salt wasting did not correlate with reduction of GFR or elevation in BUN but occurred at all levels of renal insufficiency. As corroborative evidence, the diuretic stage both of acute tubular necrosis and postobstructive uropathy [*75*] is characterized by tubular damage and sodium wasting.

SUMMARY

There is evidence to support both major theories in various types of renal disease. Previous postulations of pathophysiology have erred in attempting to be too inclusive. Although there is reason to doubt the functional importance of the many bizarre nephron forms described by pathologists in disease, the presence of severe polyuria, early defects in renal concentrating ability, hyperchloremic acidosis and sodium wasting (occurring alone or together) characterize pathologic states in which tubular damage predominates over whole nephron destruction. The inflexibility of function which characterizes renal insufficiency may be a product of many factors: decrease in total functioning nephrons, diminished physiologic reserve of tubular transport, alterations in gross renal architecture and the presence of impotent nephrons.

STANLEY S. FRANKLIN, M.D.
JOHN P. MERRILL, M.D.
Department of Medicine,
Peter Bent Brigham Hospital
and Harvard Medical School,
Boston, Massachusetts

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Clinical Studies

Renal Tubular Disease with Muscle Paralysis and Hypokalemia*

EDWARD E. OWEN, M.D. *and* JOHN V. VERNER, JR., M.D.
Durham, North Carolina

TEN patients have been seen at Duke Hospital who exhibited muscle paralysis and hypopotassemia in association with renal tubular disease. Nine had classic renal tubular acidosis and another had an as yet unclassified renal tubular disease with alkalosis. Since only thirteen cases could be collected from the literature with the triad of renal tubular acidosis, hypokalemia and muscle paralysis [*1–9*], the finding of nine such patients in one institution suggests that the combination may occur more commonly than is generally appreciated. All ten patients responded well to treatment and have had no further paralytic episodes or deterioration in renal function. The purpose of this report is to describe the clinical features demonstrated by these patients, to discuss etiology and mechanisms of the disease, and to emphasize the importance of early diagnosis and treatment.

CASE REPORTS

CASE I. F. T., a thirty-nine year old white woman, was admitted to Duke Hospital on December 29, 1949, because of muscle paralysis and coma. She had been in good health until six months prior to admission when polyuria and polydipsia developed following an uncomplicated pregnancy and delivery. She recalled having had two transient attacks of muscle weakness in the five months prior to admission. These cleared spontaneously over a twenty-four to forty-eight-hour period. The attack leading to her hospitalization began forty-eight hours prior to admission as generalized weakness which progressed and was followed by dysphagia, dysphonia, nausea, vomiting, quadriplegia and semicoma.

On examination the blood pressure was 118/60 mm. Hg and the pulse rate was 80 per minute. Respirations were of the "fish-mouth" type and no diaphragmatic motion could be detected. The circulation was hyperactive, with bounding arterial pulses, capillary pulses in the nail bed, and "pistol-shot" sounds over the large arteries. There was a flaccid quadriplegia with total areflexia. The lids were ptosed bilaterally, and there was a divergent strabismus together with absent corneal reflexes, right facial weakness, absent bowel sounds, urinary incontinence, and poor responsiveness to questioning and commands.

Routine blood analysis revealed the white blood cell count to be 16,500 per cu. mm. with a slight shift to the left on differential counting. The maximal urinary specific gravity was 1.015, the pH 6.5 units, and the protein 1 plus. The blood non-protein nitrogen was 33 mg. per cent and the two-hour urinary excretion of phenolsulfonphthalein was 77 per cent. The serum potassium concentration was 1.8 mEq./L., the chloride 122 mEq./L., and the carbon dioxide combining power 15.4 mEq./L. The serum calcium was 8.5 mg. per cent with a phosphorus of 1.4 mg. per cent. An electrocardiogram showed a first degree heart block with ST and T wave changes suggestive of hypokalemia. Roentgenograms showed no evidence of osteomalacia or nephrocalcinosis.

The patient received 273 mEq. of intravenously administered potassium over a thirteen-hour period, with gradual return of muscle strength to normal. A spot urine sample obtained prior to treatment contained 85 mEq. potassium/L. During the next seven days she received 1,533 mEq. of potassium of which only 765 mEq. were excreted in the urine. At the time of discharge the only electrolyte derangement persisting was a slight hyperchloremia. The patient was completely asymptomatic. During the subsequent five years she remained well except for two documented episodes of pyelonephritis. Renal calcification was visible by x-ray examination at the end of five years. There were no further periods of paralysis or hypokalemia, but she continued to take alkalinizing solutions and potassium supplements.

Comment: This is a typical example of renal tubular acidosis (RTA). The unusual features included the extreme paralysis not only of skeletal, facial and extraocular muscles but also involvement of the smooth muscle of the bladder

* From the Department of Medicine, Duke University Medical Center, Durham, North Carolina.

and intestines. There was also a hyperdynamic quality to the circulation as well as transitory hypophosphatemia and proteinuria, all of which subsided after potassium supplementation.

CASE II. A. M., a forty-nine year old white woman, was admitted to Duke Hospital on February 12, 1951, because of flaccid quadriplegia, nausea, gagging and somnolence which had come on gradually the morning of admission. She had had recurrent episodes of pyelonephritis since the age of eighteen years as well as periodic ptosis of the left lid. Tensilon tests were negative during the times when the lid was ptosed. There was a history of polydipsia and polyuria for several years. The first attack of muscle weakness occurred thirteen months prior to admission at which time she was unable to walk for a period of eight to twelve hours. The attacks became more frequent, and at times would only involve isolated muscle groups. The episode prompting her admission was the most severe and was totally incapacitating.

On examination she was an asthenic woman with flaccid quadriplegia, hyporeflexia and lethargy. She appeared apprehensive and frightened but was otherwise normal.

The hemogram was normal. The urinary specific gravity was 1.006, the urine pH 6.5 to 7.0 units. There was 1-plus proteinuria and many white blood cells were seen in the urinary sediment. The serum potassium concentration was 1.28 mEq./L., sodium 147 mEq./L., chloride 120 mEq./L., and carbon dioxide combining power 14 mEq./L. A blood calcium was 7.7 mg. per cent, phosphorus 1.6 mg. per cent, alkaline phosphatase 1.6 Bodansky units per 100 ml., non-protein nitrogen 32 mg. per cent, and uric acid 2.6 mg. per cent. A two-hour urinary excretion of phenolsulfonphthalein was 70 per cent. The electrocardiogram showed ST-T wave changes of hypokalemia. Roentgenograms revealed bilateral nephrocalcinosis but no evidence of osteomalacia.

Treatment was vigorous, with intravenous administration of potassium and an oral alkalinizing solution. There was striking clearing of the muscle paralysis in a few hours but frank tetany appeared on the third and fourth days, with carpopedal spasm and a markedly positive Trousseau sign. The serum calcium levels were normal during the tetanic episode and the serum potassium concentration had risen to 3.3 and 3.5 mEq./L., respectively. The tetany cleared with further potassium therapy and she was discharged asymptomatic on the fifth hospital day. The serum electrolytes at the time of discharge were normal except for slight hyperchloremia.

She has been followed up for the past seven years as an outpatient and has continued to take alkalinizing solution, but supplementary potassium has not been necessary. There have been no further paralytic or hypokalemic episodes although the urine has remained persistently alkaline and hyposthenuria continues. There have been several attacks of pyelonephritis which have cleared each time after antibiotic therapy; her renal function has remained normal. The serum uric acid has remained low, a peculiarity for which no obvious explanation has been found.

Comment: The patient demonstrated typical RTA with profound potassium depletion. Following electrolyte repletion on her first admission she has remained in potassium balance without supplementary potassium. The only electrolyte medication required over this seven-year period has been the alkalinizing Shohl's solution, which suggests that possibly sodium loss, hypovolemia and secondary aldosteronism were important factors in the initial potassium depletion syndrome [*10,11*]. Marked tetany developed in the recovery period, a point of special interest.

CASE III. M. B., a fifty-five year old white woman, was admitted to Duke Hospital for the second time in August 1954 with complaints of inability to walk, sit or use her arms because of muscle weakness. Eight months prior to admission congestive heart failure developed for which she was hospitalized. She was considered at that time to have rheumatic heart disease. An electrocardiogram was normal, as were blood non-protein nitrogen, sodium, potassium and carbon dioxide combining power. She responded well to treatment with mercurials and digitalis but acute pyelonephritis developed while in the hospital, which was treated successfully with Gantrisin.® Four months prior to her second admission she first noted weakness, anorexia, easy fatigability, polyuria and polydipsia, nausea and occasional vomiting culminating in the profound muscle paralysis present at the time of her admission.

Examination revealed a chronically ill, white woman with profound muscle weakness. The blood pressure was 150/80 mm. Hg. Several hard thyroid nodules were palpable. The heart was moderately enlarged and there was a grade 3 apical systolic murmur. There was no edema and the reflexes were normal.

The hemogram was normal. Examination of the urine disclosed a specific gravity of 1.008, 1-plus protein, a pH of 5.0 units and numerous white blood cells/high power field. The blood non-protein nitrogen concentration was 79 mg. per cent, and in each liter of serum there were 123.9 mEq. of sodium, 1.8 of potassium, 82.7 of chloride and 15.2 of carbon dioxide combining power. A two-hour phenolsulfonphthalein excretion was 20 per cent and intravenous urograms showed decreased excretion but no evidence of nephrocalcinosis.

The patient was given large amounts of sodium and

potassium intravenously, with rapid and dramatic improvement. The serum electrolytes gradually returned to normal and the azotemia cleared. She was discharged after eighteen days and required no specific treatment. She was then followed in the medical clinic. Shohl's alkalinizing solution was prescribed nine months later because of the development of typical tubular acidosis with a serum chloride of 111.4 mEq./L., CO_2 combining power of 14.7 mEq./L., potassium of 2.4 mEq./L. and sodium of 130 mEq./L. The urine became more alkaline (pH of 6.5 and 7.0 units). Over the next fourteen months she required supplemental potassium as well as the alkalinizing solution but in spite of this continued to have a persistent hypokalemia and hyperchloremic acidosis, which finally cleared spontaneously. She was readmitted three years after the episode of severe paralysis and hypokalemia for evaluation of renal function. At this time there was no evidence of excessive renal excretion of sodium or potassium.

Comment: The second hospital admission of this patient was prompted by a severe deficit of both potassium and sodium due to excessive renal and gastrointestinal losses. Only later did typical renal tubular acidosis develop, which persisted for fourteen months and then subsided spontaneously. The patient appears at the time of this writing to be enjoying relatively good health and has had no further diminution in renal function.

CASE IV. P. E., a forty-five year old white woman, was admitted to Duke Hospital on May 20, 1957, because of the sudden onset, on the night prior to admission, of flaccid quadriplegia which was thought to be poliomyelitis by the local physician. She had undergone a thyroidectomy twelve years prior to admission for thyrotoxicosis but had been asymptomatic otherwise except for a two-year history of polyuria and polydipsia with nocturia three to four times and occasional dysuria.

She appeared normal on examination except for a flaccid quadriplegia and areflexia. The blood pressure was 136/56 mm. Hg and the pulse rate 80 per minute. The pulses were bounding, capillary pulses were elicited, and "pistol-shot" sounds could be heard over the large arteries. A grade 1 aortic diastolic murmur was heard along the left sternal border.

The hematocrit was 30 per cent. Blood analyses were normal. The maximal urine specific gravity was 1.016, there was 1-plus proteinuria, the pH was 7.0 units. A urine culture showed growth of Staphylococcus albus organisms. The blood non-protein nitrogen was 60 mg. per cent and the total phenolsulfonphthalein excretion in two hours was 63 per cent. The serum potassium was 1.5 mEq./L., chloride 117.6 mEq./L., and the carbon dioxide combining power was 16.9 mEq./L. The serum calcium was 8.9 mg. per cent, phosphorus 5.4 mg. per cent, alkaline phosphatase was 2.6 Bodansky units. The tubular reabsorption of phosphorus was 77 and 100 per cent on two separate occasions. An electrocardiogram showed changes of hypokalemia. The total twenty-four-hour urinary potassium excretion was 13.6 mEq. at a time when the serum potassium concentration was only 1.5 mEq./L. Roentgenograms showed no evidences of nephrocalcinosis or osteomalacia.

Over a thirty-six-hour period 1,150 mEq. of potassium were given, with complete clearing of the paralysis. The serum potassium level rose to 7.1 mEq./L., but gradually returned to normal as did the non-protein nitrogen. The only abnormalities at the time of discharge were a slight hyperchloremia of 107 mEq./L. and a persistently alkaline urine. Following discharge she has been well for thirteen months on therapy with alkalinizing solutions and potassium supplements and has had no further difficulty.

Comment: This patient showed the interesting finding of hyperkalemia following potassium administration, demonstrating the relatively fixed output of potassium that is characteristic of some of these patients [*8*]. The possibility of overloading with potassium makes it essential to perform careful serum electrolyte analyses during the treatment phase. The azotemia present on admission probably resulted from hypokalemic nephropathy [*12*].

CASE V. H. T., a forty-two year old Negro woman, was admitted to Duke Hospital on May 9, 1956, because of the sudden onset of flaccid quadriplegia. She had been well until one month prior to admission when she spontaneously aborted during the third month of pregnancy. Three weeks prior to admission stiffness of her legs developed, followed shortly thereafter by muscle weakness. Four days prior to admission she had profound weakness, fell to the ground, and was unable to move.

Examination revealed a strikingly healthy looking woman who, however, was completely paralyzed and areflexic. The hemogram was normal. The urine pH was 7.5 units, the specific gravity 1.005, and the sediment contained many white blood cells/high power field. There was 2-plus proteinuria. The two-hour excretion of phenolsulfonphthalein was 55 per cent. A serum calcium concentration was 8.6 mg. per cent, phosphorus 2.2 mg. per cent, alkaline phosphatase 1.9 Bodansky units per 100 ml., sodium 154 mEq./L., potassium 1.66 mEq./L., chloride 114 mEq./L., carbon dioxide combining power 20 mEq./L. and non-protein nitrogen 25 mg. per cent. Roentgenograms revealed no evidence of osteomalacia

or nephrocalcinosis. An electrocardiogram showed ST and T wave changes of hypokalemia.

She was given 70 mEq. of potassium intravenously during the first twenty-four hours and on the second day frank tetany developed lasting twenty-four hours. At this time the serum potassium was 2.2 mEq./L. and the calcium was 8.6 mg. per cent. The muscle strength was normal on the third day and the patient was discharged with instructions to take sodium bicarbonate 5.4 gm. per day. She was feeling well one month later at which time there was no proteinuria and her serum electrolytes were essentially normal. During the subsequent two years she has remained totally asymptomatic without supplementary potassium.

Comment: The most interesting feature here was the catastrophically sudden onset of paralysis in this patient, not previously described. The tetany was more marked than in Case II. The hypophosphatemia and proteinuria cleared with potassium replacement.

Case VI. E. C., an eight year old Negro girl, was admitted to the Pediatrics ward of Duke Hospital in February 1958 with an eight-hour history of nausea, vomiting, weakness and difficulty with walking and talking. She had had an upper respiratory infection for the seven days prior to admission and had had achondroplasia and dwarfism since birth. Her mother also was an achondroplastic dwarf but had no history of renal disease.

The patient was normotensive with a pulse rate of 76 per minute. The achondroplasia was readily apparent; she had a blank expressionless face, and could move, walk and talk only with great difficulty. Her gait was broad-based and unsteady, and the deep tendon reflexes were normal.

The hemogram was normal. The urine pH was 6.5 units, the specific gravity 1.002 and 1.004, and there was a trace of protein but no glycosuria. The blood non-protein nitrogen concentration was 28 mg. per cent, potassium 2.4, 2.3, and 3.3 mEq./L., sodium 137 mEq./L., chloride 112.1 mEq./L., carbon dioxide combining power 14.3 mEq./L. A serum electrophoretic pattern was normal, but aminoaciduria was apparent when tested with a paper chromotographic technic. A fasting and a two-hour postprandial blood sugar were normal.

She was treated with supplementary potassium with immediate and dramatic clearing of the muscle paralysis. She was readmitted in April 1958 because of flaccid quadriplegia of four hours' duration. At this time the serum sodium concentration was 142 mEq./L., potassium 2.0 mEq./L., chloride 116.9 mEq./L., carbon dioxide combining power 14.3 mEq./L., calcium 9.6 mg. per cent, phosphorus 1.5 mg. per cent and alkaline phosphatase 3.0 Bodansky units per 100 ml. She was treated again with potassium-containing and alkalinizing solutions, with rapid improvement. A twenty-four-hour urinary potassium excretion was 19.9 mEq. at a time when the serum potassium concentration was 2.0 mEq./L. There was no evidence of sodium wasting by the kidneys and a venous pH was 7.25 units. The urinary phenolsulfonphthalein excretion was 55 per cent in two hours. A Pitressin® test led to no increased urine concentration with a maximum specific gravity of only 1.010.

Comment: The presence of achondroplasia in this patient and in her mother suggested a possible relation between the cartilage disorder and the renal tubular acidosis. Urine and blood analyses were performed in family members and found to be normal. The aminoaciduria present in this case may reflect a more generalized disorder of renal tubular function. It is of interest, however, that Denton et al. have observed aminoaciduria and peptiduria in one patient with hypokalemia and acidosis which cleared completely after correction of both electrolyte abnormalities [*13*].

Case VII. S. W., a twenty-three year old Negro woman, was admitted to Duke Hospital on April 28, 1958, for evaluation of recurrent bouts of muscle paralysis. Her past history was of considerable interest in that in 1952 she was admitted to Duke Hospital with classic thyrotoxicosis treated by subtotal thyroidectomy. In 1955 she was seen in the medical outpatient clinic because of acute pyelonephritis, which responded well to treatment with Gantrisin. On both of these occasions the urine pH was acid. Five to six months prior to her last admission she began noting easy fatigability; moderate polyuria and polydipsia appeared two to three months later; and five weeks before admission she had the first of three episodes of profound muscle paralysis. Each episode began insidiously but progressed over twelve to twenty-four hours to a flaccid quadriplegia. The first two attacks subsided spontaneously after twenty-four hours and in the interval between episodes her muscle strength was normal. The third attack began three days before admission and for the first time was associated with dysphagia, somnolence and one or two episodes of vomiting.

Examination on admission revealed a chronically ill and moderately dehydrated young woman. Although she was somewhat somnolent, she was able to recall details of the history. The blood pressure was 120/70 mm. Hg, with 20 mm. of pulsus alternans. The pulse rate was 80 per minute and the respiratory rate 16 per minute. She was afebrile. All of the extremities were flaccid and she was unable to move them more than 1 to 2 inches in any direction. The trunk and neck were involved to a somewhat lesser degree. The reflexes were normal.

The hemogram was normal except for an initial leukocytosis of 18,650 cells/cu. mm. The urine was persistently alkaline, with pH ranges from 7.0 to 7.5 units. The specific gravity was never greater than 1.013, which was the admission value. Initially there was 1-plus proteinuria as well as microscopic pyuria and hematuria but these findings cleared with electrolyte replacement alone. Admission blood chemistries revealed a sodium concentration of 143 mEq./L., chloride 112.1 mEq./L., carbon dioxide combining power 16.5 mEq./L., potassium 1.9 mEq./L., calcium 11.4 mg. per cent, phosphorus 3.8 mg. per cent, alkaline phosphatase 2.6 Bodansky units, non-protein nitrogen 43 mg. per cent. The phenolsulfonphthalein excretion was 42 per cent in two hours and the blood uric acid was 2.2 and 2.6 mg. per cent. The serum total protein, albumin, globulin and cholesterol were normal. A twenty-four-hour I^{131} uptake and the protein-bound iodine concentration were normal, as was an oral glucose tolerance test. The urine during the first twenty-four hours contained a total of 33 mEq./L. of potassium. The urine amino acids were not elevated. Routine cultures were negative. A twenty-four hour urine aldosterone measured by Dr. Ralph Peterson (National Institutes of Health) by an isotopic dilution technic was 4 μg. (normal = 4 to 25 μg.). This was collected at a time when the serum potassium was normal. An electrocardiogram showed changes compatible with hypokalemia. A gastric analysis revealed histamine achlorhydria. Roentgenograms showed bilateral nephrocalcinosis but no evidence of osteomalacia. The urine titratable acidity and ammonia were persistently low.

Initial therapy consisted of intravenously administered potassium chloride. During the first eighteen hours she received 80 mEq. of potassium and noted marked improvement in muscle strength even though the serum potassium concentration was still low (2.5 mEq./L.) at the end of the infusion. She was later given oral potassium supplements as well as an alkalinizing solution. On the third hospital day she was totally asymptomatic, the muscle strength was normal and the serum potassium was 3.0 mEq./L. She received a total potassium dosage of 3,696 mEq. and had a total urine potassium output of 1,663 mEq. during the nineteen-day period of hospitalization. The serum calcium gradually returned to normal and the phosphorus, which initially was normal, decreased to a level of 2.1 mg. per cent but had also returned to normal at the time of her discharge. The serum electrolytes and non-protein nitrogen at the time of discharge were normal except for a serum chloride concentration of 107 mEq./L.

The finding of histamine achlorhydria suggested a possible generalized dysfunction of hydrogen ion production. It seemed possible that this might be secondary to carbonic anhydrase deficiency since the cells of the kidney and stomach both contain large quantities of this enzyme. The possibility of red blood cell involvement as well suggested an experimental approach. Carbonic anhydrase activity was measured in the patient's red blood cells by the method of Miller, Dessert and Rublin [*14*], together with that of twelve control subjects. The control values varied from 8.17 to 10.75, the patient's value was 9.69 enzyme units/microliter of red blood cells. The patient's alveolar arterial pCO_2 gradient was also determined and found to be normal indicating that the enzyme present was functioning normally in respect to carbon dioxide production [*15*].

Several standard oral ammonium chloride loads were given and at no time was there any effect on urine pH, titratable acidity or ammonium secretion. An oral sodium chloride load (6 gm.) had no effect on urine potassium output.

The response to sodium phosphate loading did not vary from previous reports. After 1,000 cc. isotonic sodium phosphate buffered to pH 7.4 was infused intravenously, the urine titratable acidity increased tenfold, ammonium production increased twofold, and the urine pH decreased from 7.2 to 6.44 units during the four-hour study period.

The patient's father, mother, four brothers and one sister were studied even though none had a history of renal disease. The serum electrolytes were determined in each member and the urines were measured for pH. Two brothers as well as the father had a urine pH of 7.5 units and three of the siblings had serum chlorides of 106 to 109 mEq., which is slightly above normal for this laboratory. Each member was given a standard oral ammonium chloride load and serial urines were obtained. In each member the response was normal, an increase in acidity of the urine.

Case VIII. M. W., a twenty-one year old Negro man, was first seen at Duke Hospital in 1948 at the age of twelve years. He had a long history of physical and mental retardation. Nocturia three to four times, with enuresis had long been troublesome. He had also had occasional early morning nausea and vomiting for years. Several months prior to this outpatient clinic visit he had had frequent tetanic contractions of his hands. No cause was found for his difficulties on this visit and he was not seen again until March 1952 when he was admitted with a history of weakness progressing over an eleven-day period to confusion, disorientation and semicoma.

Examination revealed a normotensive, dehydrated, poorly developed and malnourished Negro man who responded only faintly to commands. There was generalized hyporeflexia and paralysis of skeletal muscles. The hemogram was normal. The urine was alkaline with a specific gravity of 1.008. The blood showed the non-protein nitrogen to be 25 mg. per cent, calcium 8.5 mg. per cent, phosphorus 3.1 mg. per cent, carbon dioxide 58.5 mEq./L., chloride 41.3 mEq./L., potassium 1.28 mEq./L., sodium 128.2 mEq./L. and

alkaline phosphatase 1.9 Bodansky units per 100 ml. An electrocardiogram showed hypokalemic changes. The two-hour phenolsulfonphthalein excretion was 55 per cent. Intravenous pyelograms showed bilateral hydronephrosis without calcification. A bone survey revealed only that his bone age was three years behind the expected value for his age.

He was treated with large intravenous infusions of potassium chloride and sodium chloride, and within five hours was alert and began to improve rapidly and progressively. A twenty-four-hour urine potassium excretion was 107 mEq. at a time when the serum potassium was 1.60 mEq./L. He was subsequently given 30 to 38 gm. of oral potassium chloride and 6 gm. of sodium chloride/twenty-four hours in addition to large amounts of dietary potassium. A twenty-four hour urine chloride excretion was 143 mEq. when the serum chloride was 41.8 mEq./L. He was discharged asymptomatic after thirty-three days and on discharge his electrolytes were sodium 145.5 mEq./L., chloride 85.5 mEq./L., potassium 2.74 mEq./L., and carbon dioxide combining power 41.8 mEq./L.

He was then lost to follow-up until October 1955, but had been well in the interim except for polyuria, polydipsia, enuresis and occasional tetanic episodes. The serum potassium concentration at this time was 1.8 mEq./L., chloride 82 mEq./L., calcium 11.1 mg. per cent, phosphorus 3.2 mg. per cent, and sodium 145 mEq./L.

In March 1956 he was readmitted to the hospital for further evaluation, having continued in the interim between admissions to work and feel well. He was still underdeveloped and had a positive Chvostek and Trousseau sign. The hemogram was normal. The urine was alkaline, with 2-plus protein, and the specific gravity never exceeded 1.012. The carbon dioxide combining power was 29 mEq./L., chloride 84.1 mEq./L., sodium 131.9 mEq./L., and potassium 2 mEq./L. A two-hour urine excretion of phenolsulfonphthalein was 60 per cent. The blood nonprotein nitrogen was 30 mg. per cent. An electrocardiogram again showed profound changes of hypokalemia. He received 1,976 mEq. of potassium as potassium chloride during an eight-day hospitalization, in addition to the potassium present in his diet and in 240 cc. of orange juice daily. With this the serum potassium rose to 3.3 mEq./L. on the day of discharge without any change in the carbon dioxide combining power or chloride. On returning to the medical clinic ten days following discharge the serum potassium was 1.0 mEq./L. and the carbon dioxide was 43.7 mEq./L. The urine remained alkaline and, in spite of the marked drop in potassium, the patient noted no decrease in his strength or increased frequency of tetany. A twenty-four-hour urine aldosterone concentration in 1956 was found to be 200 μg. per cent measured as deoxycorticosterone equivalents. Two subsequent determinations, however, have been normal. Baseline urinary 17-hydroxycorticosteroids and 17-ketosteroids were normal but the response to ACTH administration was slightly exaggerated. On May 11, 1956, the serum potassium was 1.6 mEq./L., carbon dioxide combining power 33.9 mEq./L., and non-protein nitrogen 29 mg. per cent. He was referred to the National Institutes of Health in November 1957 where he was again demonstrated to excrete excessive quantities of sodium and potassium in the urine regardless of any variation in intake. The urine remained persistently alkaline and dilute. It was the opinion at the National Institutes of Health that he had some form of renal tubular disease resulting in hypokalemia and alkalosis. Intravenous pyelograms at the National Institutes of Health revealed changes of nephrocalcinosis and hydronephrosis.

Comment: This patient has presented an extremely challenging problem both diagnostically and therapeutically since first seen ten years ago. He had maintained extreme degrees of hypokalemia throughout despite massive potassium supplementation, and he has persistently excreted large amounts of potassium in the urine at times when the serum level ranged from 1 to 2 mEq./L.

On his initial hospitalization, in addition to being potassium-depleted, he was shown also to excrete increased quantities of sodium and chloride. The urinary chloride was 143 mEq./twenty-four hours when the serum chloride was only 41.3 mEq./L. A marked tolerance to hypokalemia has developed in the patient as demonstrated by being ambulatory and feeling well with a serum concentration of only 1 to 2 mEq./L. He has had persistently positive Trousseau and Chvostek signs. Although he has had one increased urinary aldosterone value, it would seem unlikely that he had primary aldosteronism in view of the early age of onset, the absence of hypertension, the presence of hydronephrosis and nephrocalcinosis, and the demonstration early in his course of salt wasting. It is now believed that he has renal tubular alkalosis with periodic secondary hyperaldosteronism [*10,11*] which may be in part related to the excessive sodium and chloride loss in the urine.

Recently Borst et al. [*16*] have reported a somewhat similar patient with refractory hypokalemia and tetany. In addition, their patient also had alkalosis, alkaline urine, excessive renal potassium loss, transient hypercalcemia and normal blood pressures. Borst's patient, however, did not have the associated sodium and chloride wasting, muscle paralysis or

impaired urine concentration shown by M. W. (Case VIII).

CASE IX. I. B., a twenty-four year old white woman, was admitted to Duke Hospital on May 28, 1958, with a two-day history of progressive muscle weakness. She gave a life long history of polyuria and polydipsia. She was six months' pregnant at the time of admission. With her last four pregnancies she had had occasional periods of generalized muscle weakness lasting twenty-four to forty-eight hours. Two days prior to admission she gradually became weak and this progressed until she was unable to walk or sit alone.

Examination revealed a thin, white woman appearing much older than her stated age. The blood pressure was 105/65 mm. Hg. She had complete absence of teeth. A six months' gravid uterus was noted. The reflexes were normal, but all skeletal muscles were profoundly weak and she was unable to lift her extremities from the bed.

The hemogram was normal. The urine pH was 7 to 7.5; the specific gravity never exceeded 1.006. The blood non-protein nitrogen was 42 mg. per cent, potassium 1.8 mEq./L., chloride 114 mEq./L., carbon dioxide 16.9 mEq./L., sodium 139 mEq./L., calcium 9 mg. per cent, phosphorus 3.5 mg. per cent, alkaline phosphatase 2.0 Bodansky units, uric acid 4.1 mg. per cent, phenolsulfonphthalein urinary excretion 75 per cent in two hours. A gastric analysis revealed free acid to be present and an arterial pH was 7.3 units. Urine cultures were negative. A glucose tolerance test was normal. An electrocardiogram showed hypokalemic changes, and a spot sample of urine on admission contained 33.5 mEq./L. of potassium.

The patient was treated with potassium salts orally totalling 56 mEq. of potassium daily. There was complete return of muscle function after forty-eight hours. An ammonium chloride load of 10 gm. given orally led to no decrease in urinary acidity over a four-hour period. The serum electrolytes at the time of discharge were normal except for persistent hyperchloremia. Administration of Diamox,® 1 gm. daily, increased the twenty-four-hour urinary output of potassium from 45 to 155 mEq. and the sodium output from 35 to 122 mEq. Members of the family were studied and found to have no abnormalities by urine analysis.

CASE X. L. T., a thirty-six year old white woman, was admitted to Duke Hospital on January 13, 1958, with a one and a half year history of easy fatigability, anorexia, weight loss and periodic episodes of muscle weakness. One year prior to admission she first noted polyuria, cold intolerance, polydipsia, hair loss, constipation, decreased sweating, dry skin, numbness of hands and feet, and intermittent carpopedal spasm. She was admitted to a local hospital and after preliminary study there was referred to Duke Hospital with the presumptive diagnosis of Addison's disease. The past history was significant in that she had had pyelonephritis with several of her pregnancies.

She appeared chronically ill with marked generalized weakness. The blood pressure was 85/60 mm. Hg, the pulse rate was 60 per minute and regular. Chvostek and Trousseau signs were not present. The skin was dry, with changes of carotenemia. The thyroid gland was not palpable and the liver descended 2 fingerbreadths below the right costal margin. Deep tendon reflexes showed a slow relaxation phase and there was pallor of the nail beds and mucous membrane.

The hemoglobin was 8 gm. per cent, hematocrit 25 per cent, red blood cells 2.58 million/cu. mm., reticulocyte count 1 per cent. The white blood cell count was 3,850/cu. mm. with 48 per cent polymorphonuclear cells on differential counting. The urine pH was 7.0 units and the specific gravity 1.006. There was a trace of proteinuria and 10 to 15 leukocytes/high power field in the sediment. A urine culture grew out Escherichia coli organisms. The blood non-protein nitrogen was 28 mg. per cent and the two-hour urinary excretion of phenolsulfonphthalein was 25 per cent. A serum sodium was 135 mEq./L., potassium 2.8 mEq./L., chloride 116.2 mEq./L., carbon dioxide combining power 17 mEq./L., calcium 8.0 mg. per cent, phosphorus 2.3 mg. per cent, alkaline phosphatase 2.8 Bodansky units, total proteins, albumin and globulin normal, and cholesterol 250 mg. per cent. A twenty-four-hour I^{131} uptake was 15 per cent, the protein-bound iodine was 1.7 μg., and the basal metabolic rate was −25 per cent. A chest roentgenogram revealed no abnormalities, but abdominal roentgenograms showed evidence of nephrocalcinosis. Twenty-four-hour urinary 17-hydroxycorticosteroids and 17-ketosteroids were determined and found to be normal.

The patient was treated with desiccated thyroid and an alkalinizing solution containing potassium. In the eight month follow-up since discharge she has shown marked improvement in all symptoms and the serum electrolytes are now normal.

Comment: This is the only example known to us of the combination of hypothyroidism and renal tubular acidosis. It is of interest that she also had hypokalemia and hypophosphatemia, and that muscle weakness was the dominant complaint. Nephrocalcinosis was demonstrated by x-ray examination.

COMMENTS

Ten patients are reported who presented a clinical syndrome of muscle paralysis and hypokalemia in association with renal tubular disease. The major clinical, chemical and urinary findings are tabulated in Tables I, II and III.

TABLE I

CLINICAL FEATURES

Patient	Age (yr.) and Sex	History of Pyelonephritis	Nephro-calcinosis	Polyuria	Polydipsia	Tetany	Abnormal State of Consciousness	Associated Sodium Wasting	Associated Thyroid Disease	Hyperactive Circulation
F. T.	39, F	+	+	+	+	−	+	−	−	+
A. M.	49, F	+	+	+	+	+	+	−	−	−
M. B.	55, F	+	−	+	+	−	+	+	+	−
P. E.	45, F	+	−	+	+	−	−	−	+	+
H. T.	42, F	+	−	−	±	+	−	−	−	−
E. C.	8, F	−	−	−	−	−	+	−	−	−
S. W.	23, F	+	+	+	+	−	−	−	+	−
M. W.	21, M	+	+	+	+	+	+	+	−	−
I. B.	24, F	−	−	+	+	−	−	−	−	−
L. T.	36, F	+	+	+	+	+	−	−	+	−

TABLE II

BLOOD CHEMICAL FINDINGS ON ADMISSION

Patient	Sodium (mEq./L.)	Potassium (mEq./L.)	CO_2 (mEq./L.)	Chloride (mEq./L.)	Non-protein Nitrogen (mg. %)	Phenol-sulfon-phthalein (2 hr.) Excretion	Calcium (mg. %)	Phosphorus (mg. %)	Alkaline Phosphatase (Bodansky units)	Uric Acid (mg. %)
F. T.	.....	1.8	15.4	122	33	77%	8.5	1.4	...	...
A. M.	147	1.28	14.0	120	32	70%	7.7	1.6	1.6	2.6
M. B.	123.9	1.8	15.2	82.7	79	20%	9.1	3.8	1.6	...
P. E.	147	1.5	16.9	117.6	60	63%	8.9	5.4	2.6	...
H. T.	154	1.66	20.0	114	25	55%	8.6	2.2	1.9	...
E. C.	142	2.0	14.3	116.9	28	55%	9.6	1.5	3.0	...
S. W.	143	1.9	16.5	112.1	43	42%	11.4	3.8	2.6	2.2
M. W.	120.2	1.28	58.5	41.3	25	55%	8.5	3.1	1.9	...
I. B.	139	1.8	16.9	114	42	75%	9.0	3.5	2.0	4.1
L. T.	135	2.8	17.0	116.2	28	25%	8.0	2.3	2.8	...

TABLE III

URINE FINDINGS ON ADMISSION

Patient	pH	Protein	Specific Gravity	Urine Potassium	Sugar	Amino Acids
F. T.	6.5	+	1.015	85 mEq./L.	0	.....
A. M.	6.5–7.0	+	1.006	.....	0	.....
M. B.	5.0	+	1.008	.....	0	.....
P. E.	7.0	+	1.016	13.6 mEq./24 hr.	0	.....
H. T.	7.5	++	1.005	.....	0	.....
E. C.	6.5	trace	1.004	19.9 mEq./24 hr.	0	+
S. W.	7.0	+	1.013	33 mEq./L.	0	Negative
M. W.	7.0	+	1.008	107 mEq./24 hr.	0	.....
I. B.	7.0	0	1.006	33.5 mEq./L.	0	.....
L. T.	7.0	trace	1.006	.....	0	.....

Muscle paralysis was the dominant and usually the presenting complaint in all ten patients, and in every instance was related to hypokalemia. Such paralysis may result from hypopotassemia due to any cause and has been described in several different diseases. Hypokalemic paralysis may result from excessive excretion by the kidneys or gastrointestinal tract or from redistribution with a shift of the cation into cells. Renal wasting of potassium with paralysis has been noted in a variety of diseases including the Fanconi syndrome [*5,17,18*], nephrotic syndrome [*19,20*], diuretic phase of acute tubular necrosis [*21*], treatment phase of diabetic acidosis [*22,23*], primary aldosteronism [*24*], para-aminosalicylic acid and liquorice

therapy [*25,26*], "salt losing nephritis" [*27*], and following bilateral ureterosigmoidostomy [*28*]. Any disease state accompanied by profound vomiting or diarrhea may cause excessive losses of potassium with resultant hypokalemia. Profound and fatal potassium depletion has been described in association with non-insulin-secreting islet cell tumors of the pancreas [*29*]. Other more common gastrointestinal diseases manifesting hypopotassemia include sprue, pancreatic insufficiency [*30,31*], intestinal obstruction, and excessive use of laxatives [*32,33*]. Familial periodic paralysis is associated with an accumulation of potassium within the muscle cells, with a decrease in the extracellular concentration but no over-all depletion of body stores [*34–37*].

The muscle paralysis in the patients reported usually began insidiously with weakness and progressed gradually over a twenty-four to forty-eight hour period to complete flaccid quadriplegia. One patient had a sudden catastrophic onset with profound muscle paralysis and inability to move. The precise pathogenesis of the paralysis in these patients is unknown but a decreased ability to synthesize high energy phosphate bonds has been found in experimental animals depleted of potassium [*38,39*]. Another possible mechanism is an alteration in polarization of the muscle cell membrane. Whatever the mechanism of the paralysis, recovery was complete in all ten patients following replenishment of potassium stores. Unusual neuromuscular phenomena, not previously described as manifestations of hypokalemia, were observed in Case I. These included facial and external ocular muscle weakness as well as urinary incontinence. Two patients were comatose and two others were markedly somnolent during the hypokalemic phase—findings which cleared after potassium therapy.

Hypokalemia was extreme in all patients; the average serum concentration was 1.71 mEq./L. at the time of paralysis, and the patients who were placed on balance studies retained large amounts of potassium in the recovery period. The six patients in whom the urinary potassium was determined during the episode of hypokalemia all excreted excessive quantities. (Human subjects with normal kidneys excrete less than 10 mEq. of potassium/twenty-four hours when markedly depleted of potassium [*5,40–42*].) The finding of a transient hyperpotassemia in Case II following treatment illustrates the tendency of these patients to have a fixed urinary output of potassium and the real danger of overloading them during treatment [*8*].

The incidence of hypokalemia in patients with renal tubular acidosis cannot be determined, as balance studies have not been performed in most cases reported, but all nine patients reported here had severe hypokalemia. The mechanism whereby the kidneys excrete increased amounts of potassium in renal tubular acidosis is not known. It is presumably related to the defect in hydrogen ion excretion characteristic of the disorder, and to the substitution of potassium ions for missing hydrogen ions in a distal tubule cation exchange mechanism.

The diagnosis of hypokalemia was established in each patient by the presence of muscle paralysis, characteristic electrocardiographic changes, and a low serum potassium concentration. Perhaps the delayed growth and mental retardation seen in Case VIII were related to chronic hypokalemia, as growth disturbance and degeneration of epiphyseal cartilage have been described in experimental animals made potassium-deficient [*43–47*]. The findings of a hyperdynamic circulation in Cases I and IV and of pulsus alternans in Case VIII—all of which cleared with potassium replacement—suggested a cause and effect relationship. Although frequent descriptions of electrocardiographic abnormalities have appeared in the literature in association with hypokalemia [*48,49*], and there are many descriptions of pathologic changes of heart muscle at necropsy [*31,50*], the only previous account of abnormal cardiovascular signs occurring in such patients was the description of a hyperdynamic circulation in a patient with diabetic coma during a hypokalemic episode [*22*].

Since hypopotassemia has been shown to cause a vascular nephropathy in human beings [*51*], it is possible that the transient azotemia noted in Case IV was related to this. The hyposthenuria persisted in all cases even after potassium repletion, suggesting that it was due to permanent renal tubular disease and was not simply a manifestation of hypokalemic nephropathy.

There was marked urinary loss of sodium in Cases III and VIII in addition to increased potassium excretion. This phenomenon has been reported in one other patient, described by Earle et al. [*27*]. The sodium wasting was only transient in both cases, and neither required subsequent sodium supplements. However, so-

dium-restricted diets caused hyponatremia in Case VIII, suggesting that conservation mechanisms were still impaired. The increased urinary excretion of both sodium and potassium suggest increased delivery of sodium to the distal segment, with acceleration of the normal sodium and potassium cation exchange mechanism [*52*].

The ultimate prognosis of renal tubular acidosis is still unknown. Six of the ten patients reported here have been followed up for five years or longer without deterioration in renal function and with no further paralytic or hypokalemic episodes. Renal function has actually improved in several of the patients and no supplementary potassium therapy is presently needed in four others. There have been no deaths in this group and none of the patients have been incapacitated by their disease.

Although osteomalacia has been a prominent feature in other patients with renal tubular acidosis [*53–55*], it was not present in the cases reported. This probably merely reflects the limitations of clinical and radiological methods in establishing this diagnosis. Hypocalcemia was present in several of the patients and nephrocalcinosis in five, suggesting increased calcium excretion by the kidney.

The finding of hypercalcemia in one case, together with hypokalemia and tetany, was of interest since this combination has been reported in one other such patient by Elkinton et al. [*56*]. Calcium retention has been observed in patients with potassium deficiency as potassium was administered [*57*]. Unfortunately, no balance data are available which might elucidate the mechanism of the transient hypercalcemia seen in this patient.

Hypouricemia was noted in Cases II and VII, probably the result of impaired tubular reabsorption of uric acid but this abnormality cannot be substantiated without further data. The tubular dysfunction seen in Wilson's disease and in the Fanconi syndrome has been associated with low uric acid levels and in these disorders increased uric acid clearance has been documented [*58,59*].

Overt tetany was observed in Cases II, V and VIII as potassium therapy was being administered, and a prior history of tetany was obtained in Case X. Tetany has been reported rarely in association with hypokalemia in patients with sprue [*30*], non-insulin-secreting islet cell tumor of the pancreas [*29*], para-aminosalicylic acid and liquorice therapy [*25*] and in one other case of renal tubular acidosis [*5*]. Fourman noted the occurrence of tetany in experimental human subjects who had been depleted of potassium and then given potassium replacement therapy [*60*]. Engel et al. reported two hypokalemic human subjects with malabsorption syndrome in whom tetany could be produced at will by infusion of potassium salts [*30*] without a concomitant change in serum calcium concentration. Dennis et al. have observed the development of tetany in cattle grazing on winter wheat whenever the potassium-calcium ratio was increased by infusion of potassium [*61*]. Although the mechanism whereby tetany develops in hypokalemic patients is not known, Fourman was able to correlate this phenomenon best with an increased intracellular cation concentration [*60*].

The past history of surgically treated thyrotoxicosis in two cases, the presence of myxedema in one case, and the presence of thyroid nodules in a fourth case suggest a possible interrelationship between thyroid disease and renal tubular acidosis. The only reference in the literature which might be pertinent was the demonstration by Selye of a protective effect of thyroxine in preventing phosphate-induced nephrocalcinosis in rats [*62*].

Nine of the ten patients had the typical findings of renal tubular acidosis with hyperchloremic acidosis, hypopotassemia, grossly normal renal function and an alkaline urine. Case VII cannot be fully classified as yet but appears to have some form of chronic renal tubular disease with inability to conserve sodium, potassium and chloride ions.

The etiology of renal tubular acidosis has not been clearly established in the interval since the classic description of the disorder by Butler in 1936 [*63*] and the first balance studies by Albright in 1940 [*53*]. The childhood form has been attributed to a congenital defect or delay in renal tubular hydrogen ion secretion, because of onset shortly after birth, a tendency to remit spontaneously and permanently, and the failure to recognize distinct renal lesions in a few re-reported cases [*64*]. That the disease may be genetically determined in adults has been suggested by the finding of at least six families in which more than one member has been affected [*8,65–69*]. None of the patients reported here had a positive family history nor were significant laboratory abnormalities discovered in the two families studied.

A congenital or acquired deficiency of carbonic anhydrase has been suspected because of the inability to secrete hydrogen ions normally in the urine. The evidence against such a mechanism includes the demonstration in five patients of a normal response to Diamox.® There was in each case an intensification of the acidosis and elaboration of a more alkaline urine [*70*]. In Case VII the red blood cells were studied and found to have a normal carbonic anhydrase content when assayed by the method of Miller et al. [*14*]. This patient was also shown to have a normal arterial-alveolar pCO_2 gradient, suggesting adequate extrarenal carbonic anhydrase activity [*15*]. The history of prior pyelonephritis in eight of the ten patients reported would suggest that the renal tubular acidosis might be secondary to infection. It is, however, impossible to exclude an increased incidence of pyelonephritis in potassium depletion of whatever cause.

The primary abnormality in renal tubular acidosis is the inability to acidify the urine maximally. In 1940 Albright et al. postulated that the primary defect in urine acidification was inadequate hydrogen and ammonia production by the distal tubular cells. This hypothesis was based on careful balance studies which demonstrated that these patients have a persistently alkaline urine, a low titratable acidity, and a low urine ammonia output even after large ammonium chloride loads [*53*]. Latner and Burnard, however, showed in 1950 that urine titratable acidity and ammonia output could be increased considerably by giving intravenous isotonic sodium phosphate loads. This suggested that the primary defect did not involve hydrogen and ammonia production, and since increased urine bicarbonate was noted they postulated that the primary abnormality was an inability of the proximal tubules to reabsorb bicarbonate, with resultant alkaline urine, low titratable acidity, low urinary ammonia, increased chloride reabsorption and increased cation excretion [*71*]. Evidence against this hypothesis was reported in 1954 by Smith and Schreiner who were unable to increase the urine bicarbonate output by increasing the filtered load of bicarbonate by 35 per cent [*72*].

Since there is good evidence that hydrogen production is not impaired, it seems likely that the abnormal acidification process represents an impairment of hydrogen transport. A normal kidney will continue to secrete hydrogen ions against a large intraluminal gradient until the urine pH reaches approximately 4.5 units [73]. In patients with renal tubular acidosis the gradient is reduced and the cut-off pH for hydrogen ion secretion appears to be 6.5 to 7 units. With the decrease in hydrogen secretion, the excretion of other cations, such as sodium, potassium and calcium, increases, as does bicarbonate excretion. The degree of depletion of sodium, potassium and calcium varies widely. There are no reports of serious sodium deficiency. However, on the few occasions when the total exchangeable sodium was determined it was found to be low [*72*]. It is possible that sodium deficits, by stimulating aldosterone secretion, may contribute to the hypokalemia occurring in these patients [*10,11*], but the aldosterone levels were normal in Case VIII. Excessive renal loss of calcium led to nephrocalcinosis in five patients in this series.

The treatment of this disorder is directed principally toward correction of the electrolyte derangements and eradication of renal infection. The hyperchloremic acidosis can usually be adequately controlled by oral alkalinizing solutions, i.e., Shohl's solution. The dosages required vary from patient to patient and have to be regulated by frequent electrolyte determinations. The hypokalemia is best corrected with oral potassium salts when possible, but in some patients with nausea, vomiting, or alterations in consciousness, intravenous administration of potassium is required. In the latter cases careful clinical evaluation as well as frequent electrocardiograms and serum potassium determinations are necessary because some of these patients have a relatively fixed urinary potassium output and significant hyperkalemia may develop. Since there is evidence that administration of sodium enhances the cytotoxicity of hypokalemia [*74*], and occasionally leads to the development of edema in hypokalemic states [*75*], this cation should be restricted during the early treatment phase. Frequent follow-ups are desirable, not only for regulation of electrolytes but also in relation to the apparent increased incidence of pyelonephritis, which should be vigorously treated, when present, in an attempt to prevent further renal damage.

SUMMARY

Ten patients who were hospitalized because of flaccid quadriplegia and hypokalemia were found to have renal tubular disease. Nine had

typical renal tubular acidosis with hyperchloremia and persistently alkaline urine. One had an as yet poorly understood renal tubular disease characterized by excessive renal sodium, potassium and chloride loss, alkalosis, hydronephrosis, nephrocalcinosis and mental deficiency. Balance studies in several patients demonstrated a large negative potassium balance with abnormal urinary potassium losses even during hypokalemic episodes.

Other clinical and laboratory features included polyuria, polydipsia, nephrocalcinosis, hyposthenuria, hypouricemia and pyelonephritis, with occasional findings, during the hypokalemic phase, of normocalcemic tetany, hyperdynamic circulation, pulsus alternans and hypophosphatemia.

Of possible etiologic significance was the presence or history of pyelonephritis in eight patients. Histamine achlorhydria in one patient studied suggested a possible generalized defect in carbonic anhydrase activity. This patient's red blood cells were found to contain normal carbonic anhydrase activity, and her arterial alveolar pCO_2 gradient was normal at rest and after exercise. Although these results fail to support a generalized deficiency of this enzyme, they do not exclude a localized deficiency within the renal tubular cells.

Each patient responded well to potassium and alkali therapy and paralysis has not recurred. Renal function as measured by blood non-protein nitrogen, phenolsulfonphthalein excretion, urinalysis and intravenous pyelograms has remained normal in all subjects, six of whom have been under observation for five years or longer. Three patients no longer require potassium supplements, and one patient appears to have had a complete remission from her renal tubular disease.

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Periureteral Fibrosis, with a Diabetes Insipidus-like Syndrome Occurring with Progressive Partial Obstruction of a Ureter Unilaterally*

DONALD KNOWLAN, M.D., MICHAEL CORRADO, M.D., GEORGE E. SCHREINER, M.D. *and* ROGER BAKER, M.D.

Washington, D. C.

THE first two cases of ureteral obstruction by a non-specific inflammatory retroperitoneal process were reported by Ormond in 1948 [*1*]. At least twenty-two additional cases have since been recorded in the English literature and the entity has received considerable attention in the recent urologic literature [*2–19*]. Three patients with this disease have been studied at the Georgetown University Hospital in recent years. One of these patients presented with a syndrome of polydipsia, polyuria, and a clinical diagnosis of diabetes insipidus. This documentation of impaired water reabsorption in developing ureteral obstruction may complement recent studies which reflect the increasing awareness of tubular effects occurring after release of ureteral obstruction [*20*].

The purpose of the present report is to review the available literature on the unusual entity of periureteral fibrosis and to describe our own clinical experience in three cases, one of which may supply a clue to the pathologic mechanism. Plastic surgical procedures made rehabilitation possible in all three of our cases.

CASE REPORTS

CASE 1. A forty-four year old male physician was admitted to the Georgetown University Hospital in 1955, with a history of polydipsia and polyuria of three weeks' duration, and a tentative diagnosis of diabetes insipidus. At age forty-one the patient was found to have low-grade hypertension. A urogram showed blurring of the ptosis shadow and a non-functioning left kidney. The left kidney was palpable. Exploration disclosed an adenocarcinoma of the left kidney, with an extremely thick capsule of scar tissue and some fibrocytic proliferation of the posterior bed. A left nephrectomy was performed. Biopsies taken on adjacent structures and scar tissue revealed fibrocytic proliferation but no tumor tissue. The blood pressure decreased toward normal levels, and the postoperative course was uneventful.

The patient remained well until three weeks prior to this hospital admission when he noticed the sudden onset of extreme thirst in the daytime, a compulsive polydipsia at night, and progressive polyuria. Daily urine volumes increased to 4 or 5 L., with nocturnal frequency of four to ten times. During this period his blood pressure ranged between 160 to 190 mm. Hg systolic and 120 to 130 mm. Hg diastolic. The urinary sediments were repeatedly negative. Physical examination at that time revealed no abnormalities, except for hypertension (170/120 mm. Hg) and a left nephrectomy scar. The fundi showed arteriolar narrowing and spasm.

Attempted fluid restriction resulted in a urine with a specific gravity of 1.013. The protein excretion was 400 mg./twenty-four hours, and the urinary sediment contained 5 red cells and 5 to 8 white cells/high power field. Roentgenograms of the skull and long bones were normal. Hospital urinalyses revealed a quantitative protein excretion of 274 mg./day with 4 to 5 red cells, 1 to 2 white cells, occasional granular and hyaline casts. The urine specific gravity by urometer ranged from 1.013 to 1.010. The urine pH varied within the range of 5.0 to 6.4. The hematocrit was 44 per cent; the erythrocyte sedimentation rate was 34 mm./hr.; and the white blood cell count was 7,600 per cu. mm. with a normal differential. The total eosinophil count was 633. The blood urea nitrogen was 25, the calcium was 11, and the phos-

* From the Departments of Medicine and Surgery, and the Renal Laboratory, Georgetown University School of Medicine, Washington, D. C. This paper was supported in part by the John Hartford Foundation and the Georgetown Kidney Research Fund.



FIG. 1. Case 1. Retrograde pyelogram showing upper ureteral obstruction and hydronephrosis.

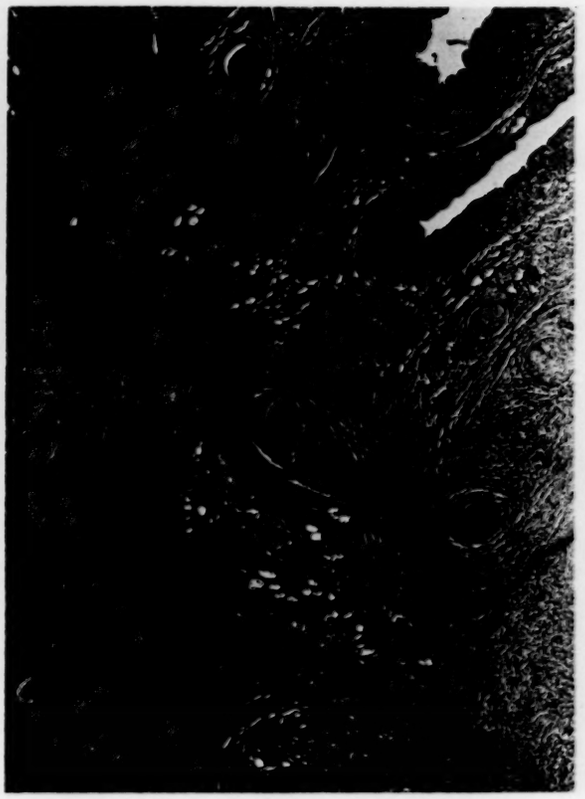


FIG. 2. Case 1. Periureteral tissue. Note the proliferation of fibrocytes and invasion of nerve sheaths.

phorus was 4.6 mg./100 ml. The serum sodium was 133, the chloride 93, and the potassium 5 mEq./L. Phenolsulfonphthalein excretion was less than 5 per cent in fifteen minutes, less than 5 per cent in thirty minutes, 10 per cent in one hour, and 10 per cent in two hours, for a total of 25 per cent. Clearance data and pitressin studies are summarized in Table 1. At cystoscopy, obstruction was encountered at 20 cm., but a small catheter was manipulated past the obstruction to the length of 27 cm. Retrograde pyelograms obtained by Dr. C. E. Bagley showed the right kidney to be large in size; the renal shadow on the left was absent. There was a markedly dilated pelvis with distention in the wall of the calyces on the right side. The ureter was narrowed. The interpretation was obstructive lesion of the right upper ureter involving a considerable segment. (Fig. 1.)

TABLE 1
CLEARANCE AND PITRESSIN DATA IN CASE 1

Measurement	Period No. 1	Period No. 2	Control*
Endogenous creatinine clearance, ml./min./1.73 M.²	50	54	....
P creatinine, mg./100 ml.	2.7	2.7	....
Urea clearance, ml./min./1.73 M.²	21	23	....
P urea	25	25	....
U mOsm.†	403	429	366
P mOsm.†	310	318	312
U/P mOsm.	1.30‡	1.35‡	1.17

* Control period taken after twenty-four hours on our standard dehydration diet.

† As determined by freezing point depression in the Bowman apparatus.

‡ After therapy with Pitressin.® (Blood pressure rose to 160/110 mm. Hg.)

In view of these data the provisional diagnosis of nephrogenic polyuria, secondary to obstruction in the upper ureter, was made. Because of the previous history of hypernephroma, extension to the contralateral side was considered likely. An exploratory operation was carried out by Dr. Frank Jones and Dr. C. E. Bagley. At the level of the second to third lumbar vertebrae the ureter seemed bound by adhesions which appeared separable. The operative excision was extended medially and anteriorly and the ureter was brought clearly into view. It was found to be surrounded laterally and posteriorly by very dense fascia, an almost "cartilaginous-like" tissue which bound the ureter firmly between the levels of L2 and L5. Large portions of this material were separated and presented for biopsy. On frozen section the material revealed extensive fibrosis and some questionable areas which later proved to be fibrocytes invading nerve sheets. (Fig. 2.) The ureter

was freed from within the fascia and much of the fibrotic capsule about the ureter between L2 and L5 was removed, and the ureter placed in a new bed. When viewed in this position the ureteral peristalsis appeared adequate. Both the anterior and posterior leaves of the fascia were extremely thickened. On the posterior aspect a deep groove was revealed, with an area of hemorrhage. This was in extremely pliable fibrotic tissue and could not be clamped or sutured, but was packed with Gelfoam.® During the surgical procedure, the patient's blood pressure dropped from 140/100 to 120/80 mm. Hg. Postoperatively the patient had a short period of oliguria. The daily urine volumes for the postoperative week were as follows: 30, 300, 800, 1,300, 1,730 and 2,760. Although the patient was on a limited liquid diet, the urinary sodium excretion was considerable, and on the fourth, fifth and sixth postoperative day was measured at 67, 80 and 39 mEq./twenty-four hours. The excretion of potassium on these days was 89, 110 and 59 mEq., respectively. The blood urea nitrogen reached a peak of 104 mg. per cent on the seventh postoperative day, but then, with increasing urine volumes, declined to normal. The patient's polydipsia disappeared immediately postoperatively, the blood pressure returned to normal, and neither the hypertension nor the polyuria has returned during the three years and two months the patient has been followed up. The excretory urogram is now completely normal.

Comment: We believe that this patient represents an unusual type of periureteral fibrosis with an associated diabetes insipidus-like syndrome that is unique in the English literature. It is noteworthy that at the time of the original nephrectomy, which would date the present illness by three years, the operative notes stressed the unusually thick fibrous capsule surrounding the histologically proved renal adenocarcinoma, presumably representing a response to the presence of this tumor. It is also noted that some retroperitoneal fibrosis was present at that time. Upon recurrence of symptomatology three years later, attention was first given to the possibility of contralateral spread or metastases from the hypernephroma. Instead an unusual instance of ureteral obstruction was demonstrated to arise from spread of fibrocytic proliferation from the anterior and posterior leaves of the renal fascia with the formation of a vise-like cuff several centimeters thick around the upper third of the ureter. Although the fibrocytes appeared unusually proliferative and were seen invading nerve sheets, there was clearly no invasion of the ureter, and when stripped free of its vise-like sheath, there appeared to be no disturbance of ureteral function. This case is of unusual interest because of its accompanying nephrogenic syndrome of hypertension, polydipsia and polyuria. The tubular defect in the reabsorption of water during a progressively developing incomplete ureteral obstruction is reminiscent of the tubular defects in water and salt reabsorption that have recently been studied after release of urinary tract obstruction [*20*].

Case II. A fifty-four year old white man was admitted to the Georgetown University Hospital for the first time in February 1955, with pain in the left side of three days' duration. Two months prior to admission the patient had intermittent cramping lower abdominal pain radiating laterally to the iliac crests. The pain occurred every two or three days and lasted two days. This pain was accompanied by abdominal distention and excessive flatulence.

One month prior to admission the patient was studied at another hospital. Intravenous pyelography led to the conclusion that there was a slight "functional disturbance of the genito-urinary tract" and a transurethral prostatectomy was performed. Following surgery the patient complained of stress incontinence. Three days prior to admission sharp severe pain in the left flank developed, radiating into the left lower quadrant. A flat plate at another hospital suggested an abdominal aortic aneurysm and the patient was transferred here for vascular evaluation. The excretory urogram at this hospital was normal.

Previous operations included an appendectomy and a transurethral resection one month prior to this admission. In recent months the patient had noted persistent lower abdominal pain. A gastrointestinal cause was sought but never demonstrated.

Physical examination revealed a blood pressure of 160/80 mm. Hg in a well developed, well nourished white man, who had a grade 3 apical systolic murmur and a liver palpable 3 cm. below the costal margin. There was a low grade fever and recent weight loss.

Urinalysis on several occasions revealed a trace of albumin and 8 to 9 white cells, with a positive glitter cell preparation. The specific gravity measurements of the urine ranged from 1.004 to 1.013. The hematocrit was 38 per cent and the erythrocyte sedimentation rate was 40 mm./hour. The white blood count was 15,000 per cu. mm. The blood urea nitrogen was 9, the fasting blood sugar was 99 per cent. The serum total protein was 7.0 gm./100 ml. of which 3.4 gm. was albumin and 3.6 gm. was globulin. The serum alkaline phosphatase was 4.0 Bessie-Lowry units and the serum acid phosphatase was 0.1 unit. The serum uric acid was 3.1 mg./100 ml. A bromsulfalein test revealed 10 per cent retention after forty-five minutes. The urine culture was negative twice; on two other occasions following retrograde examination, pseudomonas was grown in the broth but the smear was negative. Phenolsulfonphthalein excretion was 10

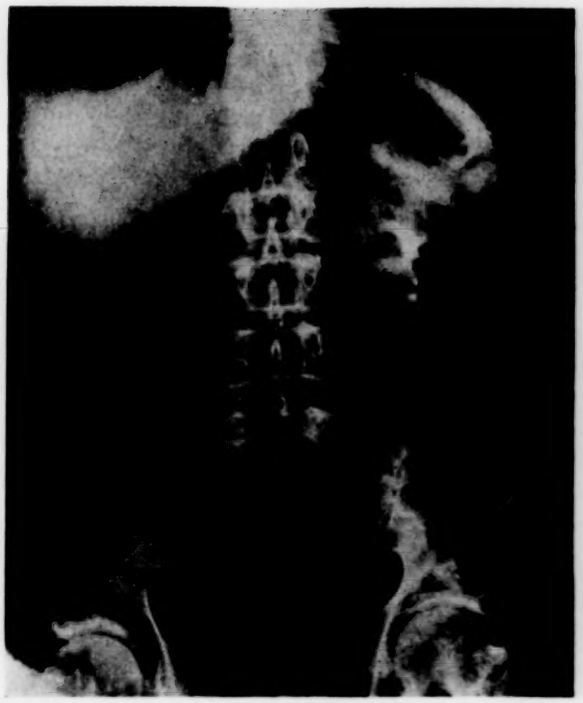


FIG. 3A. Case II. Retrograde pyelogram shows obstruction of left ureter with large kidney and dilated calyx.

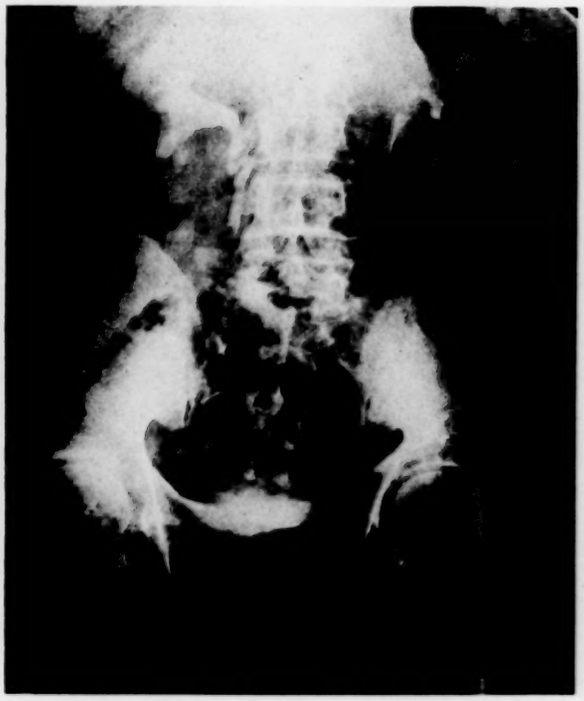


FIG. 3B. Same case. Excretory urogram shows right hydronephrosis. Note postoperative improvement in left kidney.

per cent in fifteen minutes with a 45 per cent total in two hours.

Chest roentgenogram revealed slightly emphysematous lungs. Plain film of the abdomen was unrevealing. The aorta was calcified but not enlarged. Retrograde pyelograms revealed an enlarged left kidney and slightly dilated left calyces with the suggestion of partial obstruction of the left ureter. (Fig. 3A.)

The diagnosis was left-sided pyelonephritis with hydronephrosis, and the patient was discharged for a period of prolonged antibiotic therapy. His appetite remained poor, with a weight loss of 20 pounds. Sudden nausea and vomiting developed, coincident with complete anuria which persisted for three days, and he was readmitted to the hospital April 20, 1955.

Physical examination at this time revealed a blood pressure of 140/80 mm. Hg. The patient appeared chronically ill, rather pale, but in no distress. There was a mass in the left upper quadrant that was thought to be kidney. The spleen was also palpable 3 cm. below the left costal margin. The urine revealed many leukocytes and a positive glitter cell preparation. The hematocrit was 36 per cent and the blood urea nitrogen was 42 mg./100 ml. Pseudomonas was obtained on urine culture. Catheters were passed up both ureters and excellent urine flow was obtained from both sides. The pyelonephritis improved with antibiotic therapy.

On May 6, 1955, the patient underwent exploration. The left ureter was found to be involved in thick indurated tissue along its entire course. The ureter and aorta were contained in a common fibrous sheath. A biopsy was obtained and the ureter was freed of the fibrous tissue. While most of the ureter then appeared to be normal, a 3 cm. segment was exceedingly narrowed. This long stricture was split longitudinally through all layers. A No. 12 T tube was inserted in the ureter above the incised area, and one arm of it extended through the full length of the opened ureter. No attempt was made to close the ureter over the splinting catheter. The incision was closed with the T tube and a drain in place. The pathological report revealed a chronic inflammatory process and marked fibroblastic proliferation. The postoperative course was uneventful. The T tube was clamped on May 29, and the patient was discharged May 31, to be followed up with the T tube in place. The splinting T tube was removed in late July, eight weeks postoperatively. The patient was readmitted for the fourth time September 13, 1955, for follow-up intravenous pyelogram and cystoscopy. Moderate right hydronephrosis was seen. (Fig. 3B.) The patient was discharged on September 14, to be followed up.

On September 21, 1955, the patient was readmitted for the fifth time for right ureteroplasty because of progressive right hydronephrosis. On the day prior to this admission the patient had sharp, severe right flank pain that was persistent and associated with a fever of 103°F. Physical examination revealed a blood pressure of 110/60 mm. Hg with generalized abdomi-

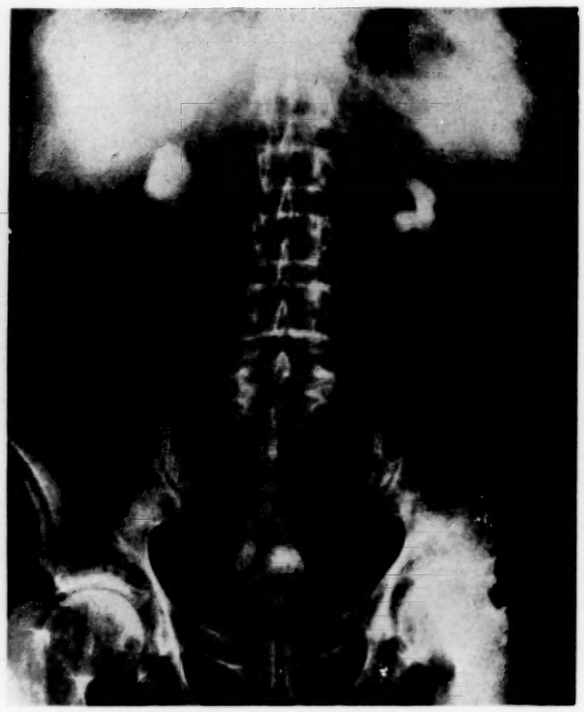


FIG. 3C. Case II. Excretory urogram showing marked right hydronephrosis.

nal tenderness and guarding. Urine cultures revealed a pseudomonas. Marked right hydronephrosis was seen on roentgenogram. (Fig. 3C.)

The pyelonephritis was treated prior to surgery. On October 5, 1955, the patient was explored and a right pyeloureteroplasty was performed. It appeared as if the entire perirenal area was involved in a fibrotic reaction. The ureter, difficult to find, was located lying in a dense thick rigid fibrous sheath involving the ureter and inferior vena cava to the left of the common iliac vessels. The ureter was freed, split, and a T tube inserted and the wound closed. The patient's postoperative course was uneventful and he was discharged November 4, 1955. The T tube was removed eight weeks postoperatively.

The patient was readmitted in December 1955 and again in April 1956. Retrograde pyelography revealed only minimal dilation of the right and left pelvis and calyces. The urine was sterile.

On July 16, 1957, the patient was readmitted for the eighth time because of pain in the left calf of ten months' duration. The picture was one of intermittent claudication of a progressive nature. The arterial pulsations on the left side were diminished. Endarterectomy was performed in the left femoral artery. The patient was discharged. At the time of discharge the blood urea nitrogen was 14 mg. per cent. The urinalysis was normal. He is now working, normotensive, and apparently completely well. The urinalysis has remained normal to the present time, which is two and a half years since his last hospital admission.

Comment: Case II apparently represents progressively developing periureteral fibrosis as a complication of bacterial pyelonephritis. Pseudomonas was the only organism cultured but the patient had repeated bouts of fever and chills, with hypertension, weight loss and splenomegaly (the last not uncommon in chronic pyelonephritis). It is curious that in the early course pain in the flank and gastrointestinal complaints dominated the clinical picture [*21*]. It was not until sudden anuria, presumably resulting from ureteritis and inflammatory edema, that the magnitude of the ureteral obstruction was really appreciated. The diagnosis of ureteritis was apparent after urine flow was improved by ureteral catheterization and the segmental obstruction could be demonstrated. Plastic surgery in this case involved bridging of an unusually long segment of diseased ureter by regeneration of ureter around a splinting catheter. Unlike Case I, the ureter was itself involved in the fibrocytic proliferation, and the lumen was narrowed to pencil point diameter. The diseased ureter was therefore split, and, using a modified T tube as a splint, a new ureter was grown around the T tube which was left in place. This resulted in remarkable improvement in the roentgenographic appearance and apparently made it possible to eradicate completely the chronic smoldering pyelonephritis, another example of the role of obstruction in the etiology and perpetuation of pyelonephritis. While the patient was under observation progressive periureteral fibrosis occurred on the contralateral side and resulted in obstruction and hydronephrosis on the right. The same type of plastic procedure was carried out on the right side and has resulted in the apparently complete rehabilitation of this patient. It is now more than three years since the original diagnosis of periureteral fibrosis and two and a half years since his last operation. The involvement of the ureteral wall with inflammatory processes suggests that pyelonephritis and ureteritis played a part in the etiology of this case of periureteral fibrosis.

CASE III. A seventy-five year old white male attorney was admitted for the first time to the Georgetown University Hospital on November 11, 1957, with a complaint of fever of ten weeks' duration. Ten weeks prior to admission the patient had noted the onset of severe shaking chills, followed by fever of 104°F. He was hospitalized and was treated with streptomycin and a broad-spectrum antibiotic after three blood

cultures were positive for a pseudomonas. A chest roentgenogram was reported as revealing pneumonia. Following discharge from the hospital the low grade fever persisted, and he again received a fourteen-day course of antibiotics. The fever persisted, with a 15-pound weight loss and anorexia. He has had constipation, hesitancy in initiating urination, and decreased force in the stream of several years' duration.

The physical examination revealed a slightly pale white man, appearing chronically ill, with a grade 2 apical systolic murmur and frequent extrasystoles. The prostate was considerably enlarged, a benign hypertrophy. There were huge bilateral inguinal hernias.

The urine specific gravity ranged from 1.007 to 1.020. There were 1 to 2 white blood cells/high power field on microscopic examination. The hematocrit was 38 per cent, the white blood cell count ranged between 19,000 and 29,000 per cu. mm. with a normal differential. The blood urea nitrogen was 9 mg./100 ml., and the serum acid phosphatase was 0.5 units. The urological tract was normal.

During a second hospital admission for fever, fatigue, anorexia and further weight loss, a mass was palpated in the left abdomen. A hidden malignancy was suspected but could not be demonstrated. Except for slight pyuria and leukocytosis, complete diagnostic studies, including x-ray studies of the gallbladder and chest, upper gastrointestinal series and an intravenous pyelogram, were unrevealing.

The patient was readmitted to this hospital for the third time in January 1958, with a history of 30 pounds weight loss since the onset of the present illness. The mild low grade fever had persisted. Physical examination revealed a temperature of 100°F. in a well developed, well nourished, pale, chronically ill white man. Examination of the abdomen revealed an ill-defined mass to the left of the umbilicus, about 10 cm. long. It could not be outlined except in its lateral position.

Laboratory results included a urine with specific gravity ranging between 1.010 and 1.018. The urine albumin ranged from trace to 3 plus. Examination of the urine sediment revealed 5 to 10 white blood cells/high power field and 16 to 17 white blood cells/high power field on another occasion. The erythrocyte sedimentation rate was 29 mm./hour. The hematocrit was 29 per cent, the white blood cell count was 20,000 per cu. mm. without a shift to the left. The fasting blood sugar was 99 mg./100 ml. The serum alkaline phosphatase was 2.0 (Bessie-Lowrey) units. The blood urea nitrogen was 20 mg./100 ml. The serum sodium was 143 and the potassium was 5.1 mEq./L. Stool guaiac was a trace on one occasion and negative on three others. The electrophoretic protein pattern in the serum was within normal limits. Urine culture revealed no organism on smear, but a pseudomonas was grown out of the broth. Blood cultures on two occasions grew out Bacillus subtilis, but otherwise



FIG. 4. Case III. Left hydronephrosis with ureteral obstruction.

were normal. An upper gastrointestinal series revealed a small ulcer in the cardia of the stomach.

Intravenous pyelogram revealed poor excretion of dye in the left kidney. There was obliteration of the left psoas shadow. A retrograde pyelogram showed marked left hydronephrosis with obstruction of the left ureter by an extrinsic mass. (Fig. 4.) The patient had a low grade fever of 99 to 100°F., which rose somewhat for several days following the retrograde pyelogram. A diagnosis of retroperitoneal tumor was made.

At operation on January 28, 1958, the ureter was found to be embedded in a mass of dense fibrous inflammatory tissue extending from the lower pole and pelvis of the left kidney to the pelvic brim. Pus was expressed from the inflammatory tissue by the surgeon and was found throughout the mass. Culture obtained failed to reveal an organism on smear, but Escherichia coli was obtained from the broth. No acid-fast organisms were seen on the smear or culture. As the patient was a thin, weakened, seventy-five year old man with other diseases, and as the right kidney was normal, the entire inflammatory mass and the ureter were removed with the left kidney. The patient did well postoperatively, remained afebrile and recovery was uneventful. He was discharged in March 1958, afebrile and asymptomatic.

The pathological report of the surgical specimen revealed acute pyelonephritis in the kidney. The ureter was surrounded by chronic inflammatory

tissue with extensive fibrous proliferation. Scattered throughout the fibrous tissue were chronic inflammatory cells. The final diagnosis was chronic periureteritis.

This patient is the oldest reported with this disorder. The predominant feature was a low grade fever of unknown origin of several months' duration that later in the course was associated with an ill-defined abdominal mass and finally with ureteral obstruction. At the time of surgery malignancy was the tentative diagnosis. The patient at no time had pain, abdominal, lumbar or renal, an unusual feature [*1–19*].

REVIEW OF THE LITERATURE

These are the twenty-fifth to twenty-seventh cases in the English literature of a retroperitoneal inflammatory mass of unknown etiology encircling the ureter. Four cases reported by Vest and one reported by Houston are not included in this tabulation since the cases they report appear to differ from this condition. A case described by Miller, which involved the kidney locally, also is not included because of incomplete information.

Sex, Race and Age. Of the twenty-four cases included in this survey, excluding our own, nineteen were males and five were females. Twenty-three patients were Caucasian and one was a Negro. The average age for the group was 45.5 years. The male average age was 46.5 years, with a range of twenty-four to sixty-nine. The average age for the females in the series was thirty-two years with a range of twenty-four to fifty-six.

Chief Complaint and Duration of Symptoms. Five of the patients in the literature presented with a complaint of pain in the back of variable intensity, which in one instance radiated into both legs. Seven of the patients presented with pain in the left flank that increased in intensity, often radiated in the pattern of ureteral colic and at times was associated with abdominal pain. In six of the patients the chief complaint was abdominal pain of varying degree, usually vague at first and then of increasing intensity and of no specific location. Two patients presented with pain in the right loin and one of these had associated hematuria. In one patient the onset was with sudden anuria. One patient presented with pain in the lower extremities, two patients with edema of the lower extremities.

The duration of symptoms ranged widely, from five hours to forty-two months, with an average of 8.5 months in the nineteen cases in which this information was given. In eight of the nineteen cases the duration was four to six months; five had symptoms for less than one month, and three for more than two years.

Associated Symptoms. The most common symptoms associated with the present illness were related to the gastrointestinal system. Nine patients had associated vomiting, six complained of nausea, and two had anorexia alone. Six patients had malaise and fatigue. Weight loss of 10 to 40 pounds was a feature in four patients. Abdominal pain was an associated symptom in four, and abdominal distention in three. Four patients complained of constipation. Two patients had diarrhea, chest pain and hematuria as part of their present illness. Fever was present in only three cases. Two of the five female patients complained of excessive vaginal bleeding. Frequency, nocturia, oliguria, backache, edema, headache, dysuria, thirst and urinary burning were each part of the present illness in a single case.

Past Diseases of Significance and Previous Surgery. Two of the patients had duodenal ulcers, one each had bacillary dysentery, ulcerative colitis, reticulum cell sarcoma, marked abdominal trauma, diabetes and carcinoma of the breast, either associated with the present illness or closely related to it in time. Three of the patients had undergone cholecystectomy, one had undergone subtotal gastrectomy, and one each underwent appendectomy, hysterectomy and removal of a carcinoma of the breast. One woman had three previous normal pregnancies. In the course of the present illness, one patient had undergone laminectomy for his back pain. Two patients had colonic diverticuli.

Physical Examination. The physical examination was rarely revealing. Only three patients had significant temperature elevation, two were low grade and one marked (106°F.). The blood pressure was mildly elevated in six patients, ranging from 135 to 190 mm. Hg systolic and from 95 to 110 mm. Hg diastolic. In only one patient was a mass felt and in another a mass was suspected. Six patients presented with varying degrees of tenderness in the costal vertebral angle. Other isolated findings in single patients included associated inguinal hernia, fibroid, small inguinal and femoral nodes, transient

right hemiplegia, and jaundice. Two patients had edema of the lower extremities.

Laboratory and Roentgenograms. The hemoglobin or hematocrit was reported in twelve cases. The hemoglobin was 14 gm. per cent in one patient, in eight it ranged from 8 to 11, and in three was reported as decreased.

The urinalysis was mentioned in fifteen cases. In one patient, albuminuria was a feature, and in seven white blood cells were seen in varying number, from a few to many. In five patients, red blood cells were found in the sediment, from few to many. Two were reported as normal.

The white blood count ranged from 8,000 to 11,000 per cu. mm. in the eight reported cases. The erythrocyte sedimentation rate was elevated when reported. The blood urea or non-protein nitrogen was reported in fourteen cases. It was increased in twelve and normal in two. In one patient the blood urea nitrogen was 240 mg. per cent.

The results of urine cultures were mentioned in eight cases. Five were reported as positive, Aerobacter aerogenes appearing in three cases, E. coli in one, and proteus in one. Three cultures were negative.

The results of the intravenous pyelogram were mentioned in thirteen cases. In six of these the pyelograms were normal two weeks to six months prior to diagnosis. Two of the thirteen were reported as normal at the time of diagnosis. Five reported abnormalities of the left kidney, consisting of either obstruction, hydronephrosis or failure of the dye to be excreted. Five reported bilateral abnormalities and one had pathological changes in the right kidney.

Cystoscopy and retrograde examination were reported in twenty-two cases. In thirteen cases there were abnormal findings in both kidneys; six showed pathological changes on the left, three on the right.

Abdominal pain patterns often led to the suspicion of a gastroenterologic diagnosis. Complete gastrointestinal studies were made in eight patients and were not revealing.

Pyelonephritis. In nine cases pyelonephritis was diagnosed, either by examination of the surgical specimen or by urine culture. In no other case of the remaining fifteen was it definitely ruled out. Four of the patients had difficulty with recurrent pyelonephritis following surgery.

Anuria. Anuria was present at some stage in the course of the illness in ten patients, but absent in five. It was not mentioned in the other nine, and we may presume that it did not occur.

Type of Involvement. Both ureters were involved in fourteen cases, although not simultaneously in every instance. The left ureter alone was involved in five cases, the right alone in four. Of the fourteen instances of bilateral involvement, not always of the same degree, the involvement initially was bilateral in eleven patients and presented as unilateral involvement in three. The left side was involved initially in one, the right in two.

Number of Operations. In these twenty-four patients various surgical procedures were undertaken, totaling forty in all for the group. Five patients underwent three procedures before satisfactory results were obtained.

Methods of Treatment. Various forms of therapy were employed. Of the forty surgical procedures performed, four were bilateral nephrostomy. Twenty-one ureterolyses were performed, with removal of some or all of the fibrous tissue and freeing of the ureters. Nephrectomy was performed in four instances as the only procedure; in three others, it was performed in association with ureterolysis. X-ray therapy was undertaken in two patients. Colostomy was performed in one patient when the colon became involved in the process. One female patient underwent hysterectomy for a fibroid prior to the onset of her ureteral difficulty. Biopsy alone was performed in several instances. One patient, with previous surgery on one side, improved with antibiotics when the opposite side was involved.

Pathology. Three patients with periureteral fibrosis have died, in two of whom autopsies were performed and no associated difficulty was found. At operation in the others the involvement varied from the localized constriction of a ureter by a fibrous band as it crossed the iliac vessel, to diffuse involvement extending from the kidney into the sacrum and compromising the ureters and aorta. Microscopically one sees a chronic inflammatory reaction, with predominance of lymphocytes and marked fibroplastic proliferation. One biopsy on the third attempt revealed an associated reticulum cell sarcoma. One of the patients who presented with jaundice and was autopsied following death was found to have a fibrous band occluding the bile duct.

Follow-up. Very few follow-up observations are available (see Talbot and Mahoney's

paper [17] on this subject). They report that Miller's patient was doing well after six years. Two other patients were in good health after three years. There were three deaths. Four patients had difficulty with persistent pyelonephritis. The late results in five patients were not mentioned. Four patients were well immediately after treatment, without follow-up. Six patients who were followed up for one year were doing well.

COMMENTS

Periureteral fibrosis is a reputedly rare condition of unknown etiology involving the retroperitoneal structures, particularly the ureter and at times the aorta, and resulting in various symptoms. Many regard it as idiopathic, others consider it a vasculitis or collagen disease. The findings at autopsy in one case of a fibrous adhesion obstructing the bile duct suggests the possibility of a diffuse disease. The finding of reticulum cell sarcoma in association with it on one occasion suggests possible multiple etiologies [19]. The frequency of the association of pyelonephritis with periureteral fibrosis is striking and needs further exploration. It is not altogether clear whether the pyelonephritis is always the result of obstruction by the retroperitoneal inflammatory tissue.

A review of anatomical considerations might be helpful in determining the etiology. In 1943 Daesler and Anson [22] demonstrated by dissection in cadavers that the abdominal aorta, vena cava and ureters lie in the same fascial compartment. The para-aortic nodes, which receive drainage from many areas, lie in this space in abundant number, surrounding the aorta. These nodes receive drainage from the testes, epidydymis, vas deferens, ovary, ureter and kidney, as well as from the gastrointestinal tract through the mesenteric system. Infection present almost anywhere in the abdomen could conceivably spread here. Thus it is possible that stimuli from infection or tumor or other cause from the genitourinary tract or gastrointestinal tract, or locally, would initiate a reaction in this area that may be excessive.

We do not believe that this condition is as rare as supposed, nor idiopathic, but that it may represent an exaggerated local response in the area to many different stimuli. An interesting associated phenomenon was the involvement of the colon subsequently in one patient requiring colostomy. Ewing once described hyperplasia of the scar reaction as a sort of benign tumor which might be termed "fibrocytoma." The analogy can also be made to keloid formation which is an exaggerated local reaction to a variety of stimuli.

The unusual sequence of events in Case I may provide one clue as to the pathogenesis of periureteral fibrosis. Here previous surgery demonstrated unusual local fibrocytic proliferation in response to a malignancy. The proliferation became more extensive after removal of the initial stimulus. The process, at least in this instance, exhibited one of the qualities of true neoplasm. Direct association in the other cases with ureteritis and chronic pyelonephritis, however, suggests that the stimulus may be varied and that chronic smouldering infection may initiate the fibrocytic proliferation.

Clinically, the condition appears to predominate in middle aged white men, who usually present with a history of vague back pain or abdominal pain of several months' duration that is usually progressive. Examination at this time is usually unrevealing. Symptoms are progressive and the patients have severe colicky, usually left flank, pain that may radiate. This is associated with nausea, vomiting, weight loss and malaise. In 40 per cent of the cases the patient subsequently becomes anuric. Physical examination still is unrevealing. Anemia is a constant feature, along with varying elevations of the blood urea nitrogen. Retrograde pyelography, following abnormal intravenous pyelograms, reveals bilateral involvement in 50 per cent of the cases. Hydronephrosis or ureteral obstruction is found. In twenty-five per cent of those with unilateral involvement, involvement of the other side subsequently develops. The patient then undergoes surgery, initially nephrectomy or nephrostomy with ureterolysis on one side, and subsequently an operation on the other side with freeing of the ureter. Appropriate antibiotic therapy is necessary. The patient's postoperative course is varied. He usually is symptom-free and without abnormal findings, but may have persistent pyelonephritis. Only 12 per cent have died.

The prognosis is good with the proper therapy. As more cases appear, treatment seems to have become more conservative, although surgery is necessary for relief of obstruction. It appears that freeing of the ureter bilaterally might be all that is necessary for satisfactory results. When direct ureteral involvement is present, as in our Case II, the newer plastic procedures have much to offer.

Many ureteral gaps have been bridged; ureteral segments and even a whole new renal pelvis completely regenerated in cases observed in our Renal and Urologic Divisions. The fact that in 25 per cent of the patients with unilateral involvement symptoms on the other side developed makes one tend to the more conservative treatment initially, unless obstruction is playing a role in perpetuation of infection.

Our Case I is of particular interest because of recent studies [*20*] suggesting physiologic damage to the nephron cells as a result of urinary obstruction. The diabetes insipidus-like syndrome and impaired response to therapy with Pitressin are indicative of a nephrogenic concentration defect. The reversible hypertension presumably was of renal origin. The excessive sodium and potassium excretion postoperatively cannot be ascribed with certainty to the ureteral obstruction since there was an intervening period of oliguria.

SUMMARY

Three cases of periureteral fibrosis are reported. The impaired concentrating capacity, poor response to Pitressin and renal hypertension noted in one case suggest damage to the nephron with progressive obstruction of the urinary tract similar to that reported after release of obstruction.

Twenty-four other cases in the English literature are reviewed, with correlation of the clinical and pathologic features.

Periureteral fibrosis is conceived to be an exaggerated fibrocytic response to varied stimuli. In Case I an adenocarcinoma was probably responsible; in other cases the proliferation seemed to be a response to chronic ureteritis and smouldering pyelonephritis.

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Chronic Idiopathic Jaundice

A Study of Two Afflicted Families

ROBERT L. WOLF, M.D., MURRAY PIZETTE, M.D., ALEXANDER RICHMAN, M.D., DAVID A. DREILING, M.D., WALTER JACOBS, M.D., OSCAR FERNANDEZ, M.D. *and* HANS POPPER, M.D.

New York, New York

CHRONIC idiopathic jaundice, as described by Dubin and Johnson [*1*] and Sprinz and Nelson [*2*], has been reported in family members of fifteen of the forty-one cases in which a family history was obtained. In only two instances [*14,25*] was the presence of the disease confirmed in two family members by liver biopsy. In the present study the diagnosis of chronic idiopathic jaundice was established by liver biopsy in several members of two families. This provided the opportunity to study different degrees of the disease process and to recognize the existence of mild variants of the disorder which otherwise would not be established.

Chronic idiopathic jaundice is characterized by icterus and the presence of an abundance of an unidentified pigment in the hepatic parenchymal cells. The clinical, laboratory and pathologic differences between this disorder and Gilbert's disease have been repeatedly emphasized [*1–4*]. Gilbert's disease is characterized by the insidious onset of chronic or intermittent jaundice frequently aggravated by intercurrent disease, early age of onset, high familial incidence, fatigue, dyspeptic symptoms, occasional liver enlargement, hyperbilirubinemia due to an increase in free bilirubin giving the indirect van den Bergh reaction, and normal appearance of the liver on both gross and microscopic examination [*3–11*]. The disease described by Dubin and Sprinz and subsequent investigators also is characterized by insidious onset at an early age and chronic or intermittent jaundice but is distinguished from Gilbert's disease by the following features: hyperbilirubinemia due to the presence of bilirubin glucuronide giving the direct van den Bergh reaction; high incidence of bilirubinuria; frequent abnormal values of the bromsulphalein, thymol turbidity and cephalin flocculation tests; frequent failure to visualize the gallbladder by oral cholecystography; and an abnormal dark appearance of the liver due to accumulation of an unidentified pigment in the hepatic parenchymal cells [*1,2,12–20*].

CASE REPORTS

Family I

CASE 1. D. R. was well until the age of twenty-six when, in June 1957, he noted the appearance of fever, abdominal distress in the right upper quadrant, dark urine, light colored stools, generalized pruritus and jaundice. He was admitted to another hospital where the clinical diagnosis of infectious hepatitis was made. His symptoms diminished in severity and jaundice disappeared almost completely during the subsequent five months in the hospital on a regimen of bed rest, vitamins and a high calorie, low fat diet. He was still icteric at the time of discharge, and two weeks later pain in the right upper quadrant, fever, dark urine, light colored stools and pruritus recurred. His jaundice deepened, and in December 1957, he was admitted to The Mount Sinai Hospital.

Physical examination showed a well nourished, well developed Puerto Rican man with moderate scleral icterus, an erythematous "butterfly" eruption over the face, and slight tenderness to percussion over the liver area anteriorly. The following examinations were performed, with normal results: urinalysis, complete blood count, erythrocyte sedimentation rate, reticulocyte count, blood urea nitrogen, fasting blood sugar, serum amylase, serum proteins, serum and hemoglobin electrophoresis, blood coagulation profile, chest roentgenogram, barium examination of the upper gastrointestinal tract, secretin test of pancreatic function, serum alkaline phosphatase, cholesterol, glutamic oxaloacetic acid transaminase, thymol turbidity test, and urine urobilinogen. Bile was present

* From the Departments of Medicine, Pathology and Surgery, The Mount Sinai Hospital, New York, New York.
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in the urine, the serum bilirubin was 5.0 mg. per cent, of which 2.0 mg. per cent was bilirubin glucuronide, the cephalin flocculation test was 3 plus, and the gallbladder visualized well on oral cholecystogram. A blood Wassermann test, three L.E. preparations, a direct Coombs' test, and a rectal biopsy for Schistosoma ova were all negative. Biopsy of the face lesion revealed chronic discoid lupus. The patient was given a high calorie, low fat diet and kept at bed rest. His symptoms gradually disappeared, the stools returned to their normal color, and the urine became lighter in color although bilirubinemia and icterus persisted unchanged. The cephalin flocculation test became negative three weeks after his admission to the hospital.

Although the diagnosis at the time of admission seemed to be that of chronic hepatitis, the persistence of hyperbilirubinemia and bilirubinuria while the other liver function tests were in the normal range and the patient was gaining weight and becoming asymptomatic prompted further study. After two percutaneous aspiration biopsies of the liver, the patient was informed of the benign nature of his disease, and was discharged from The Mount Sinai Hospital while still icteric in February 1958. During this same period, other members of his family were admitted to The Mount Sinai Hospital for study.

CASE II. V. R., a thirty-five year old brother of patient D. R., had suffered from slight fatty food intolerance for three years, and during the year prior to admission had become aware of slight scleral icterus. There was no history of passage of dark urine or light colored stools. His general health was good and he did not seek hospitalization until his brother was found to have chronic idiopathic jaundice. At the time of admission to The Mount Sinai Hospital in February 1958, he was found to be a well developed, well nourished white man with moderate scleral icterus, no abdominal tenderness and no hepatomegaly. The following examinations were all normal: chest roentgenogram, complete blood count, urinalysis, erythrocyte sedimentation rate, blood urea nitrogen, fasting blood sugar, serum amylase, secretin test of pancreatic function, Quick prothrombin time, thymol turbidity test, cephalin flocculation test, serum proteins, alkaline phosphatase, blood coagulation profile, serum glutamic oxaloacetic acid transaminase, urine urobilinogen and a bromsulphalein test of hepatic function. A blood Wassermann test, L.E. preparations, stool examination for ova and parasites, and rectal biopsy for Schistosoma ova were all negative. Bilirubinuria was present; the serum bilirubin was 3.0 mg. per cent, of which 1.7 mg. per cent was bilirubin glucuronide. The gallbladder visualized only faintly on oral cholecystogram.

CASE III. C. R., the eighteen year old sister of patient D. R., was admitted to The Mount Sinai Hospital in February 1958. She had been completely well and was unaware of any jaundice. On physical examination she was a well developed, well nourished white girl with slight scleral icterus, no hepatomegaly and no abdominal tenderness. Chest roentgenogram, complete blood count, urinalysis, erythrocyte sedimentation rate, blood urea nitrogen, fasting blood sugar, serum amylase, secretin test of pancreatic function, serum proteins, serum glutamic oxaloacetic acid transaminase, alkaline phosphatase, cholesterol, Quick prothrombin time, thymol turbidity test, and cephalin flocculation test were all normal. A bromsulphalein test of hepatic function revealed 26.5 per cent dye retention after forty-five minutes. The gallbladder visualized well on oral cholecystogram. The serum bilirubin was 3.6 mg. per cent, of which 1.7 mg. per cent was bilirubin glucuronide.

CASE IV. C. R., a twenty-three year old brother of patient D. R., had been aware of scleral icterus since childhood. In other respects his health had been good. He was a "weekend drinker" and had noted deepening of scleral icterus and darkening of his urine after each period of alcoholic excess. His stools never had been light colored, nor had he experienced intolerance for fatty foods, or abdominal pain. Physical examination at the time of admission to The Mount Sinai Hospital in February 1958 revealed a well developed, well nourished white man with slight scleral icterus. Normal results were obtained in the following studies: urinalysis, complete blood count, erythrocyte sedimentation rate, chest roentgenogram, blood urea nitrogen, fasting blood sugar, serum amylase, secretin test of pancreatic function, blood fibrinogen, Quick prothrombin time, Owren prothrombin time, stabile factor, labile factor, serum prothrombin activity, serum proteins, cholesterol, alkaline phosphatase, serum glutamic oxaloacetic acid transaminase, thymol turbidity test, cephalin flocculation test, urine urobilinogen, and bromsulphalein retention. Bilirubinuria was present, the gallbladder failed to visualize on oral cholecystogram, and the serum bilirubin was 3.1 mg. per cent, of which 1.5 mg. per cent was bilirubin glucuronide.

CASE V. E. R., a fifty-seven year old Puerto Rican woman, was the mother of the patients just described. Except for abdominal pain resulting in surgery for "gall stones" twenty-five years before, she had enjoyed good health. At no time had she noted icterus, dark urine or light colored stools. At the time of admission to The Mount Sinai Hospital in February 1958, she was a well developed, well nourished white woman with slight scleral icterus and a well healed abdominal scar in the right lower quadrant The liver was not palpable. Complete blood count, chest roentgenogram, electrocardiogram, urinalysis, erythrocyte sedimentation rate, blood urea nitrogen, fasting blood sugar, serum amylase, secretin test of pancreatic

TABLE I

CORRELATION OF CLINICAL AND PATHOLOGIC DATA IN FAMILY MEMBERS WITH CHRONIC IDIOPATHIC JAUNDICE

Case No.	Preceding Liver Disease	Duration of Jaundice	Serum Total Bilirubin (mg. per cent)	Urine Bile	Per cent Bromsulphalein Retention (45 min.)	Oral Cholecystogram	Degree of Liver Cell Pigment	Kupffer Cell Pigment
Family I								
I	? infectious hepatitis in June 1957	6 months	5.0	1–2 plus	6.5	Normal	+	++
II	None	1 year	3.0	1 plus	3.5	Faint visualization	+	....
III	None	Unknown	3.6	1 plus	26.5	Normal	++	....
IV	None	Since childhood	3.1	1 plus	2.0	No visualization	+++	....
V	None	Unknown	5.2	0	25.0	Absent gallbladder	++	+
Case of Dr. Ehrlich	.....	.....	...	....	....	.....	+++	....
Family II								
VI	None	Since childhood	2.7	0	8.0	Faint visualization	++	....
VII	None	Unknown	1.6	0	4.0	Faint visualization	++	....
VIII	None	None	0.3	0	1.0	Normal	±	....

function, serum proteins, serum glutamic oxaloacetic acid transaminase, cholesterol, alkaline phosphatase, thymol turbidity test, cephalin flocculation test, urine urobilinogen and Quick prothrombin time were all normal. Bilirubinuria was absent, a bromsulphalein test of hepatic function disclosed 25 per cent dye retention after forty-five minutes, and the serum bilirubin was 5.2 mg. per cent, of which 1.5 mg. per cent was bilirubin glucuronide. The gallbladder did not visualize on a double-dose oral cholecystogram.

Family II

CASE VI. C. T., a twenty-nine year old Puerto Rican housewife, had been in good health until May 1957 at which time episodes of postprandial epigastric distress appeared. During the next year these episodes recurred frequently, there was a gradual 12-pound weight loss, and in May 1958 she was referred to The Mount Sinai Hospital for evaluation. At no time had she noted dark urine or light colored stools, but since childhood her eyes had appeared "yellowish." There was no family history of jaundice or disease of the gallbladder.

On physical examination she was a thin, well developed white woman in no distress. The abdomen was soft and non-tender, the sclerae were not icteric. Chest roentgenogram, complete blood count, urinalysis, erythrocyte sedimentation rate, barium examination of the upper gastrointestinal tract, blood urea nitrogen, fasting blood sugar, Quick prothrombin time, bromsulphalein retention, serum proteins, cholesterol, glutamic oxaloacetic acid transaminase, thymol turbidity, cephalin flocculation test, alkaline phosphatase, cholesterol, serum amylase and urobilinogen were all normal. Stool examination for ova and parasites was negative. Bilirubinuria was absent, the gallbladder visualized faintly on the third day of an oral cholecystogram, and the serum bilirubin was found to be 2.7 mg. per cent, of which 1.7 mg. per cent was bilirubin glucuronide. As a result of our experience with the first family described in this report, the clinical diagnosis of chronic idiopathic jaundice was made. The patient became free of symptoms soon after admission and was discharged from the hospital to the care of her private physician in May 1958.

CASE VII. M. F., a married twenty-four year old sister of patient C. T., had always been well and denied ever having had jaundice, dark urine, light colored stools or abdominal distress. She was admitted to The Mount Sinai Hospital in May 1958. On

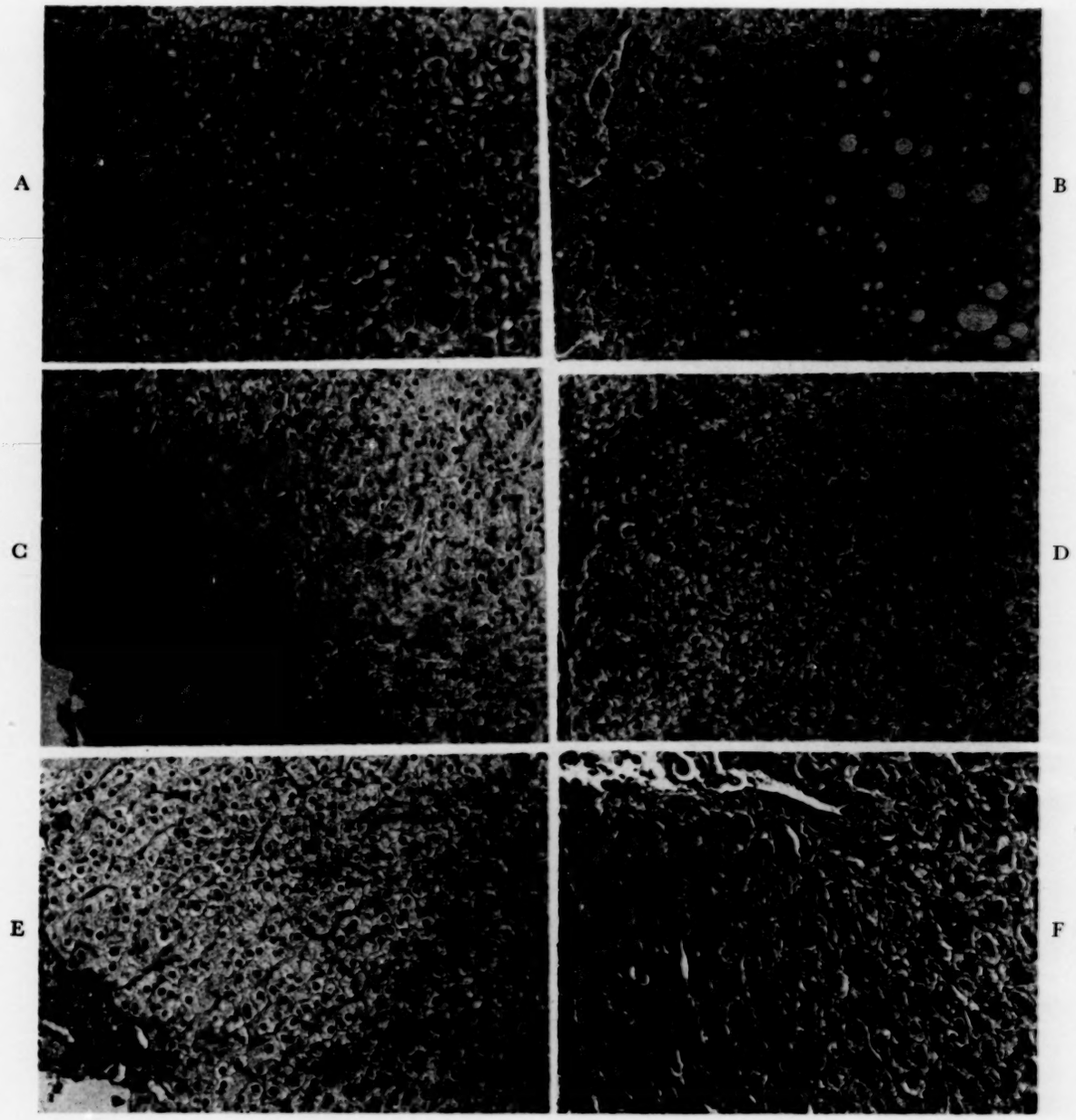


Fig. 1. Photomicrographs of liver biopsy specimens of Family I. Hematoxylin and eosin stain. Original magnification × 120. A (Case I), designated as 1-plus pigment (arrow). B (Case II), designated as 1-plus pigment (arrow). C (Case III), designated as 2-plus pigment. D (Case IV), designated as 3-plus pigment. E (Case V), designated as 2-plus pigment. F (patient from other hospital (Dr. J. Ehrlich)), designated as 3-plus pigment.

physical examination she appeared well developed and well nourished, the liver was not palpable, and icterus was not present. Chest roentgenogram, complete blood count, urinalysis, erythrocyte sedimentation rate, blood urea nitrogen, fasting blood sugar, bromsulphalein retention, serum proteins, Quick prothrombin time, glutamic oxaloacetic acid transaminase, cholesterol, alkaline phosphatase, thymol turbidity test, cephalin flocculation test, urine urobilinogen and serum amylase were all normal. Bilirubinuria was absent, the gallbladder visualized faintly on a double-dose oral cholecystogram, and the serum bilirubin was 1.6 mg. per cent, of which 1.1 mg. per cent was bilirubin glucuronide.

Case VIII. S. V., the thirty-five year old brother of patients C. T. and M. F., was admitted to The Mount Sinai Hospital in May 1958. He denied jaundice, fatty food intolerance, dark urine, light colored stools; in fact, he had always been in good health. Physical

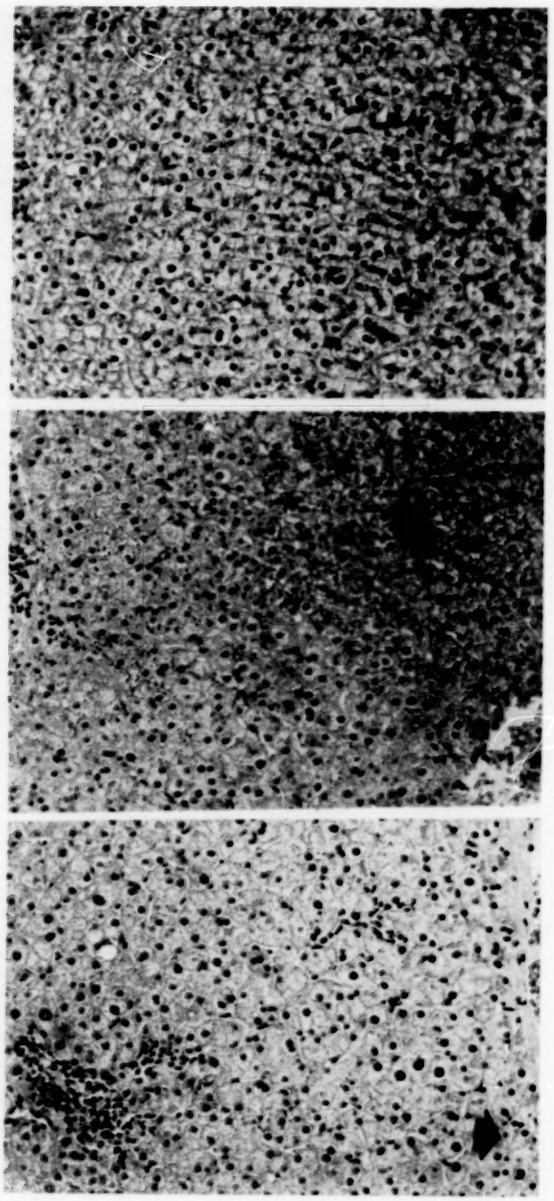


FIG. 2. Photomicrographs of liver biopsy specimens of Family II. Hematoxylin and eosin stain. Original magnification × 120. A (Case VI), designated as 2-plus pigment. B (Case VII), designated as 2 plus pigment. C (Case VIII), designated as ± pigment (arrow).

examination disclosed a well nourished, well developed white man with no icterus, hepatomegaly or abdominal tenderness. Chest roentgenogram, complete blood count, urinalysis, erythrocyte sedimentation rate, blood urea nitrogen, fasting blood sugar, Quick prothrombin time, bleeding time, clotting time, bromsulphalein retention, serum bilirubin, urine urobilinogen, alkaline phosphatase, cholesterol, serum glutamic oxaloacetic acid transaminase, thymol turbidity test, cephalin flocculation test, and serum amylase were all normal.

Needle biopsy of the liver was performed in all instances and repeated in Case I. Quite frequently the core appeared dark grey. On histologic examination, various amounts of a brown-yellow pigment were found in the liver cells in amounts arbitrarily graded from ± to 3 plus. (Table I.) One-plus designates accumulation of distinct granules of approximately 1 micron size along the bile capillaries of the liver cells in the centrolobular zone. Some of the granules were larger and measured up to 3 microns in size and exhibited sharp but not quite regular outlines. Larger granules were seen rarely. They aggregated in single cells and then extended for some distance into the cytoplasm. Grade 2 indicates aggregation of larger granules found in almost all cells of the centrolobular zone which extend sometimes throughout almost all of the cytoplasm but with a preference for the peribiliary zone, as was apparent on cross section of the bile capillary. In grade 3 the pigment deposition involved the entire lobule and extended throughout the greater part of the cytoplasm of all cells of the centrolobular zone, and the number of large granules was considerably greater. Plus-minus designates the centrolobular peribiliary accumulation of small pigment granules which could not with certainty be separated from similar pigment accumulations in normal livers. (Fig. 1.) The pigment described was in all instances bleached by hydrogen peroxide and was not acid-fast. It failed to give a sudan black reaction in paraffin section but was impregnated with silver and gave a dark brown fluorescence. The iron reaction was negative. In Case IV, traces of iron were found in the liver cells of the periportal zone, apparently not related to the brown pigment. Two members, each of Family I, exhibited 1-plus and 2-plus grades of the brown pigment. One member in this series exhibited a 3-plus change, and the same degree of abnormality was found in another member of the family who was examined in another institution. The pathologist, Dr. Joseph C. Ehrlich, kindly provided us with the slide and the report of this case. In Family II, two members had 2-plus pigment and one had ±. (Fig. 2.)

In the series examined, the brown pigment granules did not give the periodic acid-Schiff (PAS) reaction after diastase treatment, but especially in the degrees designated 1 plus, PAS-positive granules of similar size were intermixed with the brown granules. In liver specimens containing more pigment deposition, PAS-positive material was found between the granules. The PAS-positive material in the liver cells gave a distinct but low white fluorescence. The Kupffer cells contained a considerable amount of a brown pigment in Case I and small amounts in Case IV. The brown pigment in Case I gave a distinct PAS reaction, disclosing large granules about 4 microns in diameter which were especially apparent in small accumulations of intraparenchymal and portal macrophages. In other instances the Kupffer cells contained much smaller amounts of PAS-positive

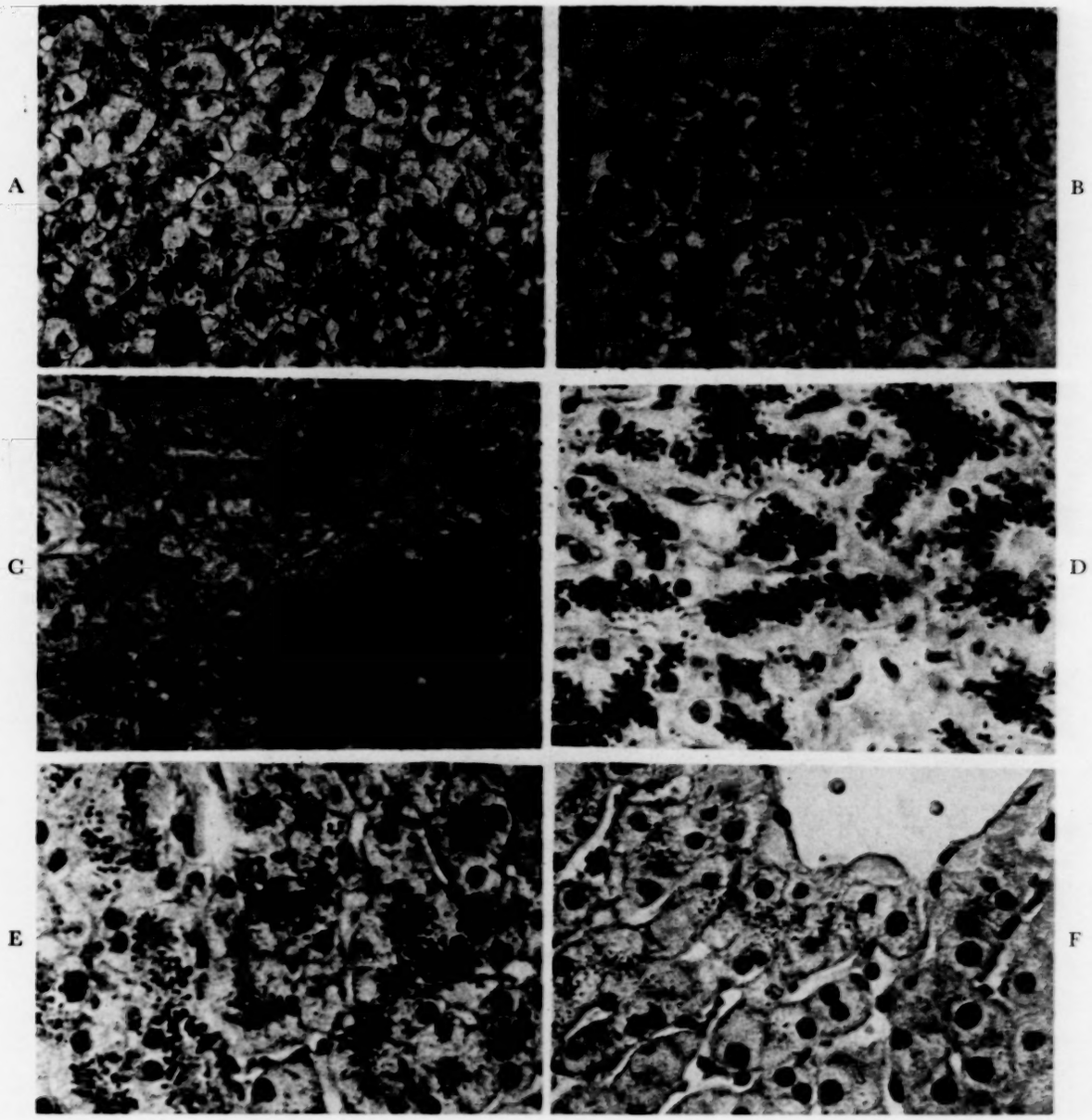


FIG. 3. Photomicrographs of liver biopsy specimens. Original magnification × 400. A (Case I), PAS stain. Large PAS-positive granules are seen in the Kupffer cells and a moderate amount can be made out intermixed with pigment granules around bile capillaries of liver cells. B (Case II), hematoxylin and eosin stain. A moderate number of granules are visible throughout the cytoplasm of liver cells and along bile capillaries. C (Case III), hematoxylin and eosin stain. A large number of granules, varying in size, can be seen around bile canaliculi and irregularly distributed throughout cytoplasm. D (Case III), PAS stain. A large number of PAS-positive granules intermixed with pigment granules are visible around narrow bile capillaries and Kupffer cells. E (Case IV), hematoxylin and eosin stain. A large number of granules of various size are seen around the bile canaliculi and also diffusely spread through cytoplasm. F (Case VIII), hematoxylin and eosin stain. Small amounts of chiefly small granules can be made out around the bile canaliculi in the centrolobular zone of liver cells.

material which gave a bright white fluorescence, particularly in Case I. Only these large granules in Case I stained deep blue with aniline blue, were acid-fast and reacted markedly with astra blau, as is characteristic for acid mucopolysaccharide. In this instance, particularly, and less so in others, the PAS-positive liver cell granules gave a distinct astra blau reaction, as did the PAS-positive material in the Kupffer cells of almost all cases.

Bile pigment was never demonstrated and the bile capillaries appeared narrow. Portal inflammatory reaction with proliferation of ductular cells was found

TABLE II

LABORATORY DATA IN FAMILY MEMBERS WITH CHRONIC IDIOPATHIC JAUNDICE

Case No., Patient and Sex	Serum Bilirubin (mg. per cent)		Serum Proteins (gm. per cent)		Alkaline Phosphatase (King-Armstrong Units)	Blood Data				
	Total	Direct	Albumin	Globulin		Total Cholesterol (mg. per cent)	Cholesterol Esters (mg. per cent)	Thymol Turbidity (units/cc.)	Cephalin Flocculation	Transaminase (units/cc.) (20–40)
Family I										
I, D. R., M	5.0	2.0	4.7	3.4	8.0	190	140	2.2	0	36
II, V. R., M	3.0	1.7	4.8	3.2	7.2	180	150	3.8	0	17
III, C. R., F	3.6	1.7	4.9	2.8	6.1	148	128	1.8	1+	21
IV, C. R., M	3.1	1.5	5.5	2.4	6.1	150	135	1.0	1+	20
V, E. R., F	5.2	1.5	4.6	3.1	8.0	195	152	1.5	1+	21
. . . A. R., F	0.1	0	4.3	3.4	9.5	160	145	1.7	0	23
. . . D. R., M	0.4	0.3	4.0	3.5	7.5	210	150	2.5	0	21
. . . L. R., M	0.9	0.1	4.8	2.9	9.1	130	105	3.4	1+	14
. . . I. R., F	3.6	1.6	4.8	3.5	5.3	215	200	1.4	0	6
. . . J. R., F	3.1	3.1	4.6	2.7	6.2	155	140	1.7	0	14
Family II										
VI, C. T., F	2.7	1.7	4.5	3.3	6.0	175	120	2.3	2+	25
VII, M. F., F	1.6	1.1	4.1	3.5	6.5	147	91	1.7	2+	23
VIII, S. V., M	0.3	0.1	4.6	3.6	7.3	204	148	1.0	0	45
. . . J. V., M	0.3	0.1	4.1	3.1	7.2	189	114	3.1	1+	67

TABLE III

SECRETIN RESPONSE DATA IN FIVE FAMILY MEMBERS WITH CHRONIC IDIOPATHIC JAUNDICE

Case No.	Total Volume (ml./kg.)	Bicarbonate, Maximum Concentration (mEq./L.)	Total Amylase (units/kg.)	Biliary Flow
I	3.6	94	28.8	Normal
II	3.6	96	7.2	Normal
III	4.7	113	16.9	Normal
IV	5.0	110	12.5	Normal
V	2.8	97	24.6	Absent gallbladder
Normal. . . .	2.0–5.5	90–140	6.0–18.0	. . . . .

TABLE IV

HEPATIC UPTAKE OF RADIOIODINATED ROSE BENGAL IN FIVE FAMILY MEMBERS WITH CHRONIC IDIOPATHIC JAUNDICE

Case No.	Maximum Time of Hepatic Uptake (min.)	Excretion Half Time (min.)
I	50	330
II	60	300
III	30	420
IV	40	200
V	26	45

conspicuously in Cases I, IV and VIII. Portal fibrosis was conspicuous in Cases I, II and V. Intraparenchymal focal necroses were noted in Cases V and VIII. Fatty metamorphosis was found in the central zone in Case II. Ballooning of the nuclei because of glycogen deposition was encountered in Cases II, V and VI, mobilization of the Kupffer cells in Cases I, VII and VIII, and aggregation of eosinophils in the portal space in Case I. (Fig. 3.)

The only abnormal laboratory findings were elevation of free and glucuronated serum bilirubin, the occasional occurrence of bile in the urine of Family I and the increased bromsulphalein retention in some instances. (Table II.) Oral cholecystography gave positive results in all cases in which the gallbladder was present, except in Case IV with the highest hepatocellular pigment content. In many of the others, even with slightly elevated serum bilirubin, visualization was faint.

Secretin tests [*21*] were performed in five members of Family I. The secretin response data are reproduced in Table III and are normal. The biliary pigment response in the secretin test (Table III) was also normal in all tested patients except E. R., who had previously undergone cholecystectomy [*22*]. In these patients the blood glucose response to intravenous glucagon (2.0 mg.) administration also was normal [*23*].

The hepatic uptake of radioiodinated rose bengal was measured in five members of Family I. (Table IV.)

The value of the test in the recognition of minor degrees of liver injury is undetermined but the results appear to parallel the results of other hepatic function studies now in common use [*24*]. Although our experience is limited, it appears that a normal person probably will achieve a maximum hepatic uptake value in less than thirty-six minutes, and that this value will be reduced to half within two hours after it was obtained (excretion half time). As Table III indicates, the three male siblings had a slow maximum hepatic uptake and a delayed excretion half time. The excretion half time was delayed in the female patient C. R., and the test was normal in the mother E. R.

The thymol turbidity and cephalin flocculation tests were normal in all members of both families. The Rumpel-Leede test, bleeding time (Ivy), coagulation time (Lee and White), retraction time of the blood clot (Lee and White), plasma fibrinogen (Ratnoff), plasma-prothrombin level (Owren), factors I and VII (Owren) were normal in all patients tested.

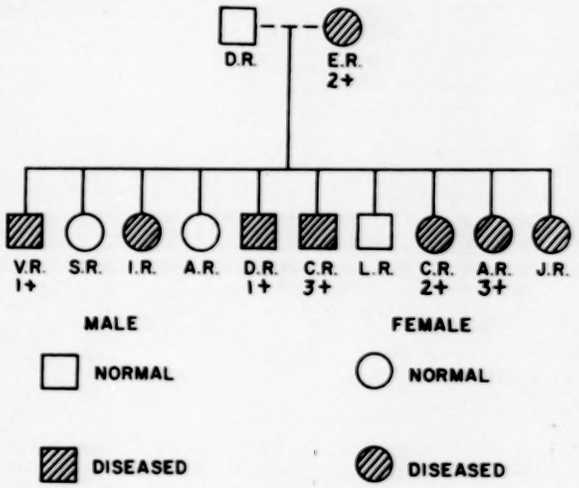


FIG. 4. Family I.

COMMENTS

Family I reported in this communication is comprised of both parents and ten siblings. Data are presented on all of the members of Family I, except two daughters. One daughter resides in Puerto Rico and was unavailable for investigation. The other daughter, who is jaundiced, was studied in another hospital where a liver biopsy was diagnostic of "Dubin-Johnson syndrome." All of the family members were natives of Puerto Rico. There was no history of jaundice or symptoms referable to the disease in the relatives. Of the eight family members with the disease, jaundice developed in two in early childhood and jaundice developed in one each at the ages of twenty-five and thirty-three years, respectively. (Fig. 4.) The remaining five family members were unaware of the presence of jaundice. All of the members studied were asymptomatic except two. One had abdominal pain, nausea, vomiting and weakness; the other had abdominal distress after eating fatty foods.

Family II consists of both parents and their six children. Four of these siblings were investigated; the remainder of the family were unavailable for study. All the members of this family were born in Puerto Rico. Of the three

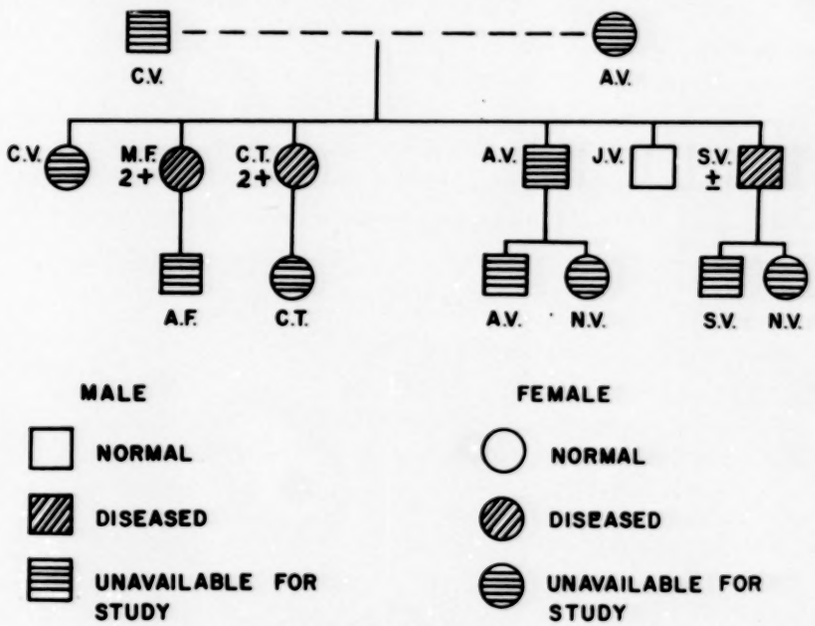


FIG. 5. Family II.

known family members with the disease, only one reported jaundice since childhood. This patient had had mild abdominal distress for one year. All of the remaining family members investigated were asymptomatic and there was no family history of jaundice or symptoms referable to the disease. (Fig. 5.)

In contrast to reports in the literature [*1,2, 12–20*], the flocculation tests were uniformly normal in these cases, and oral cholecystography was not always unsuccessful. Pancreatic and radioiodinated rose bengal studies, recorded here, have not been previously reported.

The major interest of the presented series lies in the gradation of the pigment deposition. One case (Case IV) of this series, and the one sibling examined by Dr. Ehrlich, would have been diagnosed without any hesitation as chronic idiopathic jaundice on the basis of the findings at liver biopsy. Cases III and V of Family I, and VI and VII of Family II clinically represent a mild variety of chronic idiopathic jaundice, whereas Cases I and II could at most be suspected to belong to this group, in view of their being siblings of persons with fully established chronic idiopathic jaundice. Such patients, in whom slight pigmentation of the liver cells can be demonstrated in the presence of jaundice, and who have normal or faint visualization of the gallbladder and no abnormal bromsulphalein retention should be considered to be borderline examples of chronic idiopathic jaundice. The findings of this study thus extend the concept of chronic idiopathic jaundice.

The deposition of brown pigment as well as the presence of PAS-positive material in the Kupffer cells in Case I was possibly related to a preceding infectious hepatitis, suggested by the clinical history, and apparently was not related to the chronic idiopathic jaundice. The possibility that deposition of the pigment characteristic of chronic idiopathic jaundice (which histochemically differed from the Kupffer cell pigment) was reduced by the preceding hepatitis also has to be entertained.

The appearance and quantity of pigment deposit in Case VIII of Family II was not significantly different from that found in the centrolobular zone in normal livers [*20*]. Since the subject was a member of a family with chronic idiopathic jaundice, the deposition and character of the pigment (identical with that of normal subjects except for the occasional presence of larger pigment granules, such as are seen in large numbers in chronic idiopathic jaundice) suggests the possibility that chronic idiopathic jaundice may be associated with increased deposition of the pigment normally found in the centrolobular zone, as described by Post [*26*].

The morphologic picture of narrow bile canaliculi surrounded by granules of the pigment of chronic idiopathic jaundice suggests a difficulty in transfer of a normally occurring pigment into the bile canaliculi; a piling up of pigment rather than abnormal pigment formation in this disorder. One might speculate that the group of diseases characterized by jaundice in the absence of liver cell injury, extrahepatic obstruction or hemolysis, which also includes Gilbert's disease, intrahepatic cholestasis and represents instances of impaired handling or transport of bilirubin rather than abnormal metabolic pathways.

SUMMARY

Two Puerto Rican families are described, eight members of which were found to have varying amounts of hepatic cellular pigment on liver biopsy. Ten members were found to have hyperbilirubinemia.

The microscopic appearance of the liver in one instance, and in another family member examined in another hospital, presented the fully developed picture of chronic idiopathic jaundice. In four instances a mild degree of pigment deposition was found and in two a borderline increase of the same pigment was noted. In one anicteric member the amount and distribution of pigment varied only slightly from the normal. It would therefore appear that some members of families with chronic idiopathic jaundice may have only a borderline increase in pigment.

The conspicuous hepatic pigment demonstrated in chronic idiopathic jaundice results from accumulation of a pigment present in small amount in the centrolobular zone of normal livers.

Bromsulphalein retention and oral cholecystography are not necessarily abnormal where accumulation of the pigment characteristic of chronic idiopathic jaundice is not greatly in excess, even in the presence of jaundice. Hepatic and pancreatic function tests may be entirely normal.

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Familial Chronic Idiopathic Jaundice (Dubin-Sprinz Disease), with a Note on Bromsulphalein Metabolism in this Disease*

E. Mandema, M.D.,† W. H. de Fraiture, M.D.,‡ H. O. Nieweg, M.D. *and* A. Arends, M.D.

Groningen, The Netherlands

Chronic idiopathic jaundice was first described by two groups of workers, Dubin and Johnson [*1*] and Sprinz and Nelson [*2*]. Recently Dubin reviewed the case histories of the first recorded fifty patients with this new disease [*3*], twenty-three of whom were studied by Dubin personally. The clinical picture is now well defined.

The purposes of this paper, which deals with five such patients, are to delineate more clearly the familial occurrence of this condition, and to report our observations on bromsulphalein metabolism in this disorder.

CASE REPORTS

Case I. H. S., a forty-four year old man, was first seen in the outpatient department in 1951. Jaundice had first been noticed ten years previously. He had no other symptoms. There were no significant findings on physical examination except for slight jaundice. A diagnosis was not made. Four years later he was hospitalized because of attacks of gross haematuria. He was found to have a papilloma of the urinary bladder which was cauterized. In 1957 he was readmitted for investigation of the jaundice, again with no other complaints. He stated that the jaundice sometimes became deeper without apparent cause. The urine was always dark. He never had pale stools. His father, a sister, and one of his brothers also gave a history of jaundice.

The liver and spleen were not palpable. Urinalysis occasionally gave slightly positive reaction for bilirubin. The reaction for urobilinogen was 2 plus. The blood picture was normal. The values for serum bilirubin ranged between 2 and 4 mg./100 ml. serum. The direct reaction of Hijmans van den Bergh was positive. The values for serum cholesterol, total lipids, neutral fat, phospholipids, alkaline phosphatase, zinc sulphate turbidity, SGOT and SGPT were all within normal limits. The thymol turbidity was 5 units on one occasion, but on numerous other occasions was normal. The serum iron was 112 γ/100 ml. The serum total protein was 7.76 gm./100 ml. serum, of which 61.2 per cent was albumin, 3.8 per cent α_1-globulin, 16.3 per cent α_2-globulin, 9.6 per cent β-globulin, and 11.7 per cent γ-globulin. Bromsulphalein retention forty-five minutes after an injection of 5 mg./kg. was 15 per cent.

The gallbladder was well visualized with oral contrast dye and also after intravenous injection of contrast medium, but visualization was delayed until about six hours after the injection. Liver biopsy performed with a Vim-Silverman needle yielded liver tissue that appeared black in its fresh state. The histological picture of the liver tissue was characteristic for Dubin-Sprinz disease.

Case II. Pat. E. S.-B., forty years old, was the oldest daughter of eight children. Her parents were both normal, but three brothers were icteric (Cases III, IV and V). Jaundice was first noticed at the age of fourteen, while she was suffering from an acute febrile disease, the cause of which remained unknown and for which she was admitted to another hospital. She was deeply icteric. The liver was palpable about 4 cm. below the costal margin; the spleen was not palpable. The urine contained bilirubin, and the reaction for urobilinogen was strongly positive.

Four years later (March 1936) she was admitted for the first time to our hospital. At that time she was pregnant. After the first episode of jaundice she had had many other attacks.

On physical examination she was jaundiced, but otherwise no abnormal findings were noted. The fundus of the uterus reached the costal arch. Urinalysis revealed bile pigment and 1-plus reaction for

* From the Department of Medicine and the Department of Pathology, University of Groningen, The Netherlands.
† Research Fellow, The Netherlands Organization for Pure Research (Z.W.O.). Present address: University of Illinois, College of Medicine, Chicago, Illinois.
‡ Present address: St. Joseph General Hospital, Gouda, The Netherlands.

urobilinogen. The reaction for direct bilirubin was positive, the serum total bilirubin ranged from 3 to 6 mg./100 ml. serum. No diagnosis was made. Four months later she was readmitted to our clinic. The liver and the spleen were not palpable. The gallbladder was not visualized on cholecystography which was performed four times with oral contrast medium. Once again no diagnosis was made.

At cholecystectomy performed elsewhere in 1942 no stones were found. In 1948 a liver biopsy, also performed in another clinic, revealed liver tissue with much coarse centrilobular pigment, but otherwise normal. A diagnosis was not made. In 1957 she was admitted for the third time to our hospital. She had suffered frequent attacks of pain in the right upper abdomen, with nausea and vomiting. The attacks lasted about two hours. After these attacks she became more icteric and passed dark urine. Apart from these attacks she frequently had periods of jaundice when she was cold or tired, during intercurrent diseases and during pregnancy. There were no abnormal findings on physical examination apart from a mild jaundice.

Urinalysis showed again a slight positive reaction for bile pigment and a 2-plus reaction for urobilinogen. The reaction for bilirubin was directly positive, with a serum total bilirubin ranging from 2 to 7 mg./100 ml. serum. The serum iron was 170γ/100 ml.

The values for serum total lipids, neutral fat, phospholipids and cholesterol were normal. Liver function tests including SGOT, SGPT, thymol turbidity and serum alkaline phosphatase were all within normal limits. The serum total protein was normal. The electrophoretic serum pattern was: albumin 57 per cent, α_1-globulin 5 per cent, α_2-globulin 16 per cent, β-globulin 9 per cent, and γ-globulin 13 per cent.

Bromsulphalein retention was 16 per cent, forty-five minutes after an injection of 5 mg./kg. The fecal urobilinogen excretion was 108 mg./day. She was suspected to have some kind of obstructive jaundice. At operation no obstruction was found. It was noticed, however, that the liver had a dark brown color. A biopsy revealed liver tissue with coarse centrilobular pigment granules in otherwise normal liver cells. No histological changes were found. The diagnosis of chronic idiopathic jaundice (Dubin-Sprinz disease) was finally made.

Case III. G. B. was admitted to our clinic for the first time in May 1953, at the age of thirty-two, because of colicky pains in the right upper abdomen, typical of gallstones. He became slightly icteric after the attacks and passed dark urine. Physical examination showed mild jaundice, but no other abnormalities. The liver and the spleen were not palpable. The urine did not contain bile pigment and there was only a 1-plus reaction for urobilinogen. The serum total bilirubin was 5 mg./100 ml. The direct reaction of Hijmans van den Bergh was positive. Other liver function tests were normal. With oral contrast dye, the gallbladder was not visualized; however, there were shadows suggestive of gallstones in the gallbladder region. At operation the gallbladder contained a large number of small stones. A biopsy of the liver showed a large amount of pigment around the central veins. The liver cells were otherwise normal.

After operation the patient became more deeply jaundiced at first, but some weeks later the serum total bilirubin returned to the preoperative level, and he was discharged from the hospital. When the correct diagnosis was made in his sister (Case II), the liver biopsy specimen was re-examined and the diagnosis of Dubin-Sprinz disease was made.

He visited the outpatient department on June 22, 1958, five years after cholecystectomy. He had no complaints. On physical examination there was no visible jaundice. The liver and the spleen were not palpable. The serum total bilirubin was 5 mg./100 ml., and the direct reaction of Hijmans van den Bergh was positive. The urine did not contain bile pigment. There was only a slightly positive reaction for urobilinogen. Liver function tests, including electrophoresis of serum proteins, were normal. Bromsulphalein retention forty-five minutes after intravenous injection of 5 mg./kg. was 6 per cent.

Case IV. D. B., born in 1924, had had many periods of jaundice since early childhood, without other complaints. In 1951 he was admitted to another hospital. No definite diagnosis was made, but laparotomy was performed in order to exclude biliary obstruction. At operation the bile ducts were normal, and no obstruction was found. The liver was blue-black. A biopsy was taken. The liver cells contained a large amount of pigment. No definite diagnosis was made.

He was admitted to our clinic in March 1958. Again he had no complaints. On physical examination there was mild jaundice. The liver was palpable just below the costal margin; the spleen was not palpable. Urinalysis revealed a slightly positive reaction for bile pigment and a 1-plus reaction for urobilinogen. The serum total bilirubin was 6 mg./100 ml. The fecal urobilinogen excretion was 60 mg./twenty-four hours. Liver function tests were normal. Bromsulphalein retention forty-five minutes after intravenous injection of 5 mg./kg. was 7 per cent. After intravenous injection of contrast dye the gallbladder was well visualized, but not until about five hours after the injection.

Dr. A. de Minjer, Professor of Pathology, University of Utrecht, kindly sent us the histological sections of the liver from the surgical liver biopsy of 1951, and the diagnosis of Dubin-Sprinz disease was made.

Case V. P. B., born in 1934, was admitted to our clinic in August 1956. In 1953 he had a typical gallstone colic. Afterwards he was jaundiced and passed

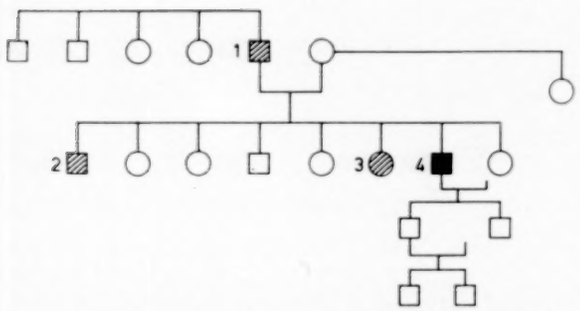


FIG. 1. Pedigree of the family of Case I (4). His father (1), a brother (2) and a sister (3) had jaundice of long standing.

dark urine. Apart from this attack he had never had any complaints. At the time of admission he felt well. On physical examination mild jaundice was found. The liver and the spleen were not palpable. The urine did not contain bile pigment; the reaction for urobilinogen was 1-plus. The serum total bilirubin was 5 mg./100 ml., and the direct reaction of Hijmans van den Bergh was positive. Liver function tests were normal. Bromsulphalein retention after intravenous injection of 5 mg./kg. was 9 per cent. The gallbladder was not visible after oral contrast dye or after a dose of 40 ml. of an intravenous contrast dye. The bile contained cholesterol crystals.

A diagnosis of cholelithiasis was made. However, after the diagnosis of chronic idiopathic jaundice had been established in two of his brothers and in one sister this case was reconsidered. The bromsulphalein disappearance curve and other changes in bromsulphalein metabolism were of the same pattern as in the four other cases, and we therefore made a diagnosis of Dubin-Sprinz disease in addition to gallstones. Because of the available evidence we did not feel justified in performing a liver biopsy.

COMMENTS

We have not been able to investigate other members of the family of Case I. With the help of his physician and an older member of his family he constructed a pedigree. This is shown in Figure 1. His father, a brother and a sister had jaundice of long standing, possibly caused by Dubin-Sprinz disease. The pedigree of the second family is shown in Figure 2. The parents, the apparently healthy brothers and sisters, and three children of the patients were examined. None of them showed abnormalities on physical examination, and all had normal serum bilirubin levels with a negative direct reaction of Hijmans van den Bergh, no increase of bromsulphalein retention, no excess of urobilinogen in the urine, and normal liver function tests. We did not find evidence of a subclinical form of the disease in these members of the family, and the difference between affected members and healthy members was always clear cut. Some other members could not be studied by us, but are known not to have been jaundiced.

In his recent paper (1958) Dubin stated that there is a tendency toward familial occurrence; thirteen of thirty-nine patients stated that one or more members of their family also were jaundiced. Familial occurrence was established three times; twice in two sisters and once in a mother and son [*4–6*]. However another example of familial occurrence in two brothers has been seen in Holland, but this has not yet been published [*7*].

Although the data available at this moment do not provide definite proof, we think it probable that Dubin-Sprinz disease is inherited in a dominant pattern, as suggested also by Beker and Read [*6*].

In two of our five patients (Cases III and V) jaundice was first noted after a typical gallstone colic. In Case III there were no complaints, although slight icterus was present after cholecystectomy, while in Case V there have been two attacks until now, but apart from this the patient had no complaints at all. Only in Case II could the complaints be ascribed to Dubin-Sprinz disease. This incidence of abdominal pain is lower than that found by Dubin, who reported that 77 per cent of his patients complained of abdominal distress.

Dubin states that gallstones were found in five of thirty patients in whom laparotomy was per-

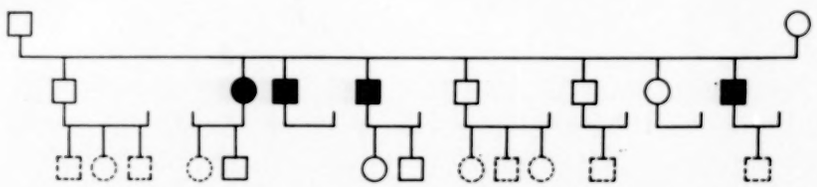


FIG. 2. Pedigree of the family of Cases II to V (black squares and circles). The solid squares and circles represent members of the family who were examined. The other members were not examined but none of them has had jaundice thus far.

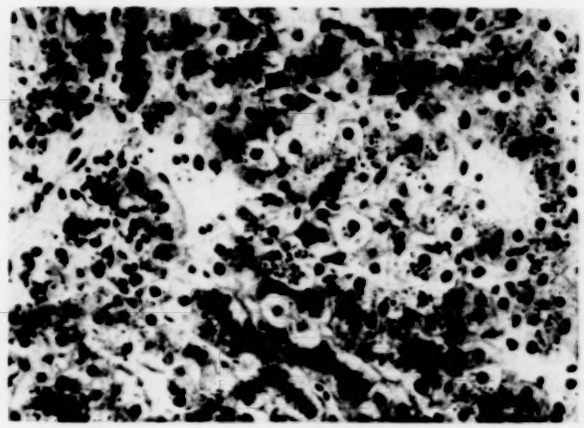


FIG. 3. High power field of a liver section of Case II, obtained in 1948. Hematoxylin and eosin stain. Original magnification × 280.

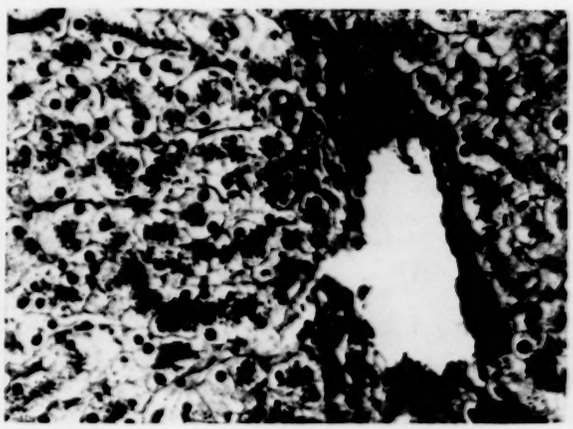


FIG. 4. High power field of a liver section of Case II, obtained in 1957. Hematoxylin and eosin stain. Original magnification × 280.

formed. Probably cholelithiasis is a rather frequent finding in chronic idiopathic jaundice. In the two patients who had escaped cholecystectomy and who were free of complaints, the gallbladder was well visualized after intravenous contrast dye, and in Case I also after oral contrast dye. It should be pointed out that the gallbladder visualized well only five to six hours after the intravenous injection of dye. In our opinion, visualization of the gallbladder in Dubin-Sprinz disease may well be possible, provided gallbladder function is good and sufficient time is allowed between the injection and the film (at least five hours). In Case II we had a liver puncture specimen of 1948 and a surgical biopsy in 1958. The amount of pigment in the liver cells was about the same. (Figs. 3 and 4.) This is consistent with a previous observation that the amount of pigment present in the liver is fairly constant [*3*].

BROMSULPHALEIN METABOLISM

Methods. Bromsulphalein was administered to fasting patients and control subjects by rapid intravenous injection in doses of 2 to 6 mg./kg. Starting three minutes after the injection, blood samples were obtained every two minutes, avoiding venous congestion; after ten minutes blood samples were obtained every three minutes, and after twenty minutes every three to four minutes, the total period being thirty or sixty minutes. Duplicate samples of 0.5 ml. serum were diluted with 10 ml. buffer solution at pH 10.7 [*8*]. The blanks were processed in an identical manner, using blood withdrawn prior to the injection. The dilutions were centrifuged for twenty minutes at 4,500 r.p.m. (about 3,000 g) immediately before spectrophotometry. At low bromsulphalein concentrations variations in the turbidity, which may occur in subsequent samples [*9*], proved to be a source of error even after centrifugation. In order to decrease this error the following correction procedure was adopted.

In addition to the dilution with buffer all samples, including the blanks, were also diluted with physiological saline solution in the same ratio. The difference between the extinction of the serum dilutions with saline and the blank serum dilution with saline was used to correct for the variation in the turbidity of the serum samples. The extinction was measured with a Zeiss spectrophotometer (M4Q) at the wave length with maximal light absorption (580 mμ.) in a 10.0 mm. test cuvet. The extinction of the serum samples diluted with buffer was measured against the blank serum dilution with buffer. This extinction was corrected by subtracting from it the difference in extinction between the serum solution in saline and the blank serum solution with saline. The corrected extinction was then compared with a standard prepared from the same batch of bromsulphalein by diluting 1 ml. (40 mg. dye) with distilled water up to 1 L., 0.5 ml. of which was diluted with 10 ml. buffer solution. Plasma dilutions both with 0.05 N NaOH and with buffer solution were more turbid than serum dilutions. The latter, therefore, were used exclusively. Hemolyzed samples were discarded.

The following methodological data were obtained: (1) Extinction was directly proportional to the bromsulphalein concentration over a range from 0 to 12 mg./100 ml. in dilutions with water and in reaction mixtures containing 0.5 ml. markedly jaundiced serum (25 mg. bilirubin/100 ml.). In a mixture with 0.5 ml. normal serum there was a slight deviation from linearity at concentrations exceeding 6 mg./100 ml. (2) The standard deviation of the determination at a concentration of 3 mg./100 ml. was 0.05 mg./100 ml. (n = 37). The standard deviation of the determination at a concentration of 0.8 mg./100 ml. was 0.02

mg./100 ml. (n = 29). (3) Bromsulphalein, added to existing concentrations below 1.5 mg./100 ml., was recovered in the presence of normal serum with an accuracy of 0.1 mg./100 ml. The accuracy of recovery of small added quantities was only slightly lower in the case of markedly jaundiced serum and at higher initial concentrations. Using this method, therefore, an accuracy of 0.1 mg./100 ml. may be assumed.

The bromsulphalein concentrations were plotted on semilogarithmic paper. In nearly all cases the logarithm of the bromsulphalein concentration decreased linearly after the first three to five minutes. The term "saturation curve" was applied when, after some time, the concentration curve, plotted in this way, deviated from linearity and followed a less sharply inclined course [*10*].

By extrapolating the linear part of the curve to zero time, t = 0, the theoretical initial concentration of bromsulphalein is determined. This is the concentration which would have been obtained if the substance were evenly distributed immediately after injection. The volume of distribution (V) was estimated by dividing the quantity of bromsulphalein injected by the initial concentration.

The quantity of bromsulphalein disappearing from the blood in an exponential manner, i.e. logarithmically linear, was calculated by multiplying the difference between the theoretical initial concentration at the point of deviation of the saturation curve, by the volume of distribution.

The slope of the linear part of the curve: the clearance coefficient—CC [*11*]—or elimination constant [*12*] was calculated by the equation:

$$CC = \frac{\log P_0 - \log P_1}{t_1 - t_0}$$

(Briggsian logarithms, time in minutes. P_0: serum concentration at time t_0. P_1: serum concentration at time t_1.

The fractional clearance—FC [*13,14*]—or percentage disappearance rate [*10*] was obtained by the same equation using natural logarithms:

$$FC = 2.3 \times CC$$

The separation of bromsulphalein metabolites in urine and bile was accomplished by ascending chromatography with butanol-water-glacial acetic acid as the solvent system. As described previously, two or three bromsulphalein fractions are found [*15*]. The fast component has the same Rf value as the injected bromsulphalein, not only in a system with butanol-water-glacial acetic acid, but also in a system with phenol-water. It represents free bromsulphalein.

The slow components with a Rf value of about half that of the fast component are bromsulphalein products, which have been conjugated in the liver. These slow fractions usually consist of two components.

The amount of the slow and fast components was determined quantitatively by extracting the bromsulphalein from the paper. We have not identified the nature of these bromsulphalein metabolites.

While our studies on bromsulphalein metabolism were in progress Krebs and Brauer published a paper on unidentified metabolites of bromsulphalein in bile, utilizing alumina columns [*16*]. The possible occurrence of bromsulphalein metabolites was stressed by the same group in an earlier paper [*17*].

Since then, other papers concerning bromsulphalein metabolites have been published by Meltzer et al. [*18*], Grodsky et al. [*19,20*], Combes [*21*], and Javitt et al. [*22*], all utilizing paper chromatography. The nature of the metabolites has not been made entirely clear, but the possibility that they are conjugates of bromsulphalein with glucuronic acid has been excluded. The metabolites appear to be conjugates of bromsulphalein with amino acids (glycine, glutamic acid and cystein) [*18–21*]. Javitt et al. think that the metabolites result from intrahepatic conjugation of bromsulphalein with glutathione [*22*].

Bromsulphalein Disappearance Curves. After the intravenous injection of bromsulphalein the concentration was estimated, as described, in blood samples taken every three to five minutes. As has been established by others, nearly all of the injected bromsulphalein is taken up by the liver and excreted in the bile [*17*]. In normal subjects only 1 to 2 per cent of the injected bromsulphalein is excreted in the urine. The uptake by the liver during the first ten to fifteen minutes occurs in an exponential manner. Thereafter the serum concentration of bromsulphalein falls more slowly. This point where the curve on semilogarithmic paper shows a deflection is called the "saturation point." A curve showing a saturation point is called a saturation curve [*10*].

We found that the amount of bromsulphalein which disappears from the blood exponentially in normal subjects is approximately constant in the same person, regardless of the amount injected, provided that a sufficient amount is injected to reach a distinct saturation point. When this quantity was calculated from the bromsulphalein disappearance curves in patients with Dubin-Sprinz disease, it did not differ significantly from the quantity found in eight normal subjects, with a saturation curve. Also, the fractional clearance of the bromsulphalein was of the same order as in normal persons. (Table 1.)

These data indicate that the uptake of bromsulphalein by the liver during the first phase, that is, the phase in which bromsul-

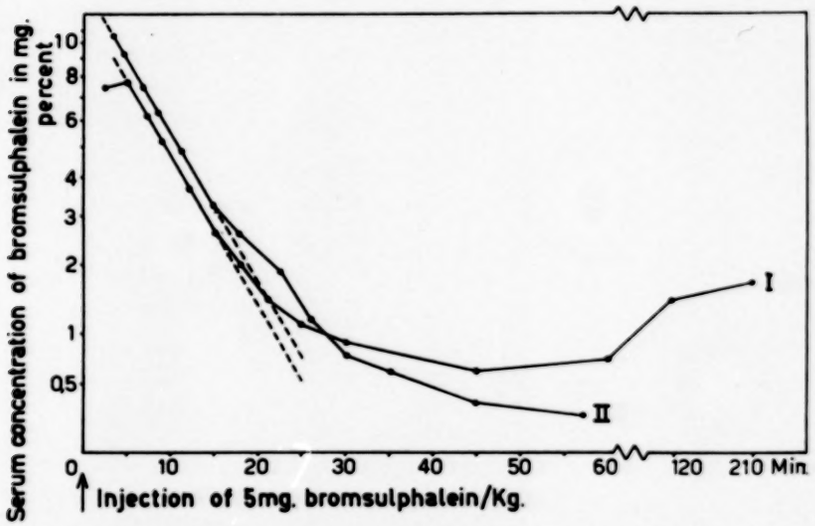


FIG. 5. Bromsulphalein disappearance curve: Case III (I), normal subject (II).

phalein is taken up by the liver exponentially, is normal in Dubrin-Sprinz disease. However, after attaining the saturation point, the concentration of bromsulphalein in patients with chronic idiopathic jaundice falls more slowly than in normal subjects, and after thirty to forty-five minutes increases. The increase was 1.12 mg./100 ml. serum in one patient. At this point, when the last blood specimen had been drawn, the curve still showed an upward slope. (Fig. 5.) In three other patients the rise in concentration was less, ranging from 0.02 mg. to 0.22 mg./100 ml. serum, but in these patients blood samples were collected for only forty-five to sixty minutes after injection. In only one patient was the blood concentration followed long enough to detect a decrease in bromsulphalein concentration. In this case the serum concentration forty-five minutes after injection was 0.61 mg./100 ml.; after 120 minutes it was 0.99 mg., and after 265 minutes 0.96 mg./100 ml. This increase in bromsulphalein has not been found in normal subjects or in patients with other liver diseases (cirrhosis, obstructive jaundice).

In our opinion, the much slower fall in concentration of bromsulphalein in the serum in patients with Dubin-Sprinz disease after the saturation point is reached strongly suggests a delay in excretion of bromsulphalein, especially of conjugated bromsulphalein, from the liver into the bile.

Meltzer et al. [*18*] believe that bromsulphalein conjugates, derived from the liver, are present in the plasma of normal persons. This may well be in Dubin-Sprinz disease; because of impaired excretion of bromsulphalein conjugates, a greater amount of these metabolites may enter the blood stream. At some point the rate at which the metabolites enter the blood exceeds the rate of movement of bromsulphalein

TABLE I

FRACTIONAL CLEARANCE AND QUANTITY OF BROMSULPHALEIN DISAPPEARING FROM THE BLOOD EXPONENTIALLY IN NINE NORMAL SUBJECTS AND FIVE PATIENTS WITH DUBIN-SPRINZ DISEASE

Subjects	Age (yr.)	Fractional Clearance	Bromsulphalein Exponentially Disappearing from the Blood (mg.)
Normal Subjects			
A. W.	25	0.121	352
H. T.	26	0.118	366
A. D.	27	0.131	Not estimated
T. S.	20	0.172	353
B. L.	17	0.099	378
G. S.	18	0.138	368
K. B.	33	0.140	372
G. K.	33	0.142	346
A. B.	62	0.133	291
Dubin-Sprinz Disease			
Case I	57	0.113	345
II	40	0.111	380
III	38	0.122	373
IV	33	0.113	345
V	23	0.133	330

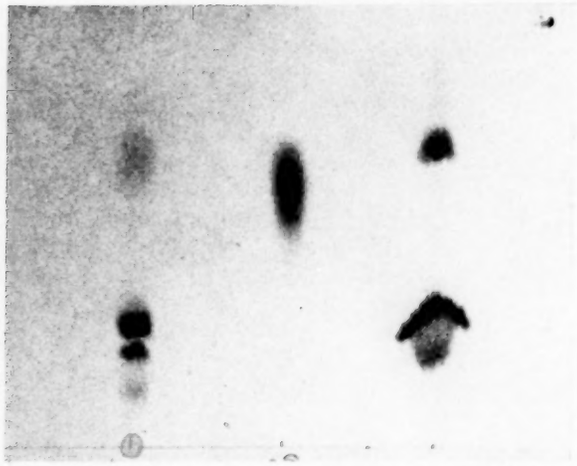


FIG. 6. Ascending chromatography of bromsulphalein excreted in the bile (left), and in the urine (right).

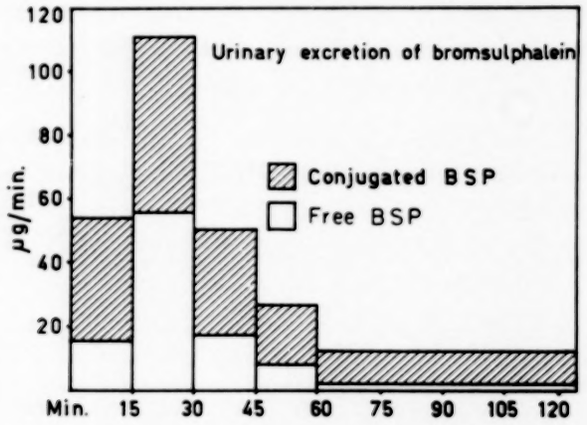


FIG. 7. Urinary excretion of bromsulphalein in normal subjects (mean of four persons) during the first four fifteen-minute periods and the second hour after injection of 5 mg./kg. bromsulphalein.

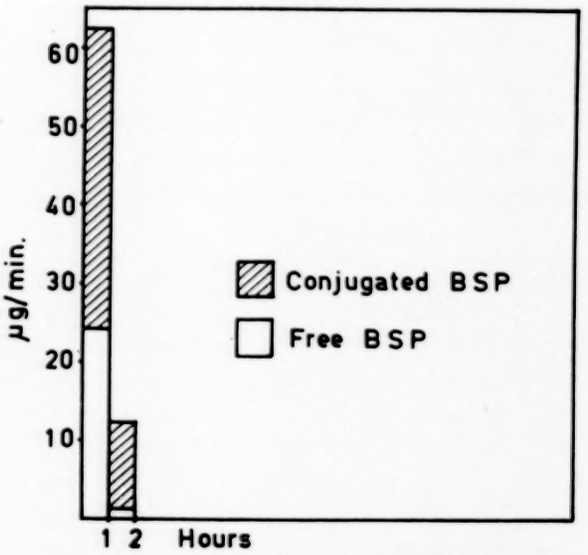


FIG. 8. Urinary excretion of bromsulphalein in the same four normal subjects as in Figure 7, during the first and second hour after injection of 5 mg./kg. bromsulphalein.

from the blood into the liver, causing the increase in serum bromsulphalein shown.

In order to detect more clearly an excess of bromsulphalein conjugates in the blood of the patients with Dubin-Sprinz disease, ascending chromatography of urine samples, obtained after the injection of bromsulphalein, was performed in the patients and in four normal subjects. These urine samples always contained some of the injected bromsulphalein, and we thought it probable that changes in the blood bromsulphalein could also be observed in the bromsulphalein excreted in the urine. The kidney in fact acts not only as a passive filter, but can also conjugate bromsulphalein to some extent, as has been proved by Grodsky [*23*]. The kidney function in our patients and in the healthy subjects was entirely normal. We therefore considered it safe to assume that changes in the urinary excretion of free and conjugated bromsulphalein reflect to a greater or lesser extent changes in the amount of free and conjugated bromsulphalein in the blood.

Chromatography of Bromsulphalein in Urine. The method has been described in more detail elsewhere [*15*]. It was found that urinary bromsulphalein could be separated into three components in an ascending chromatographic system using butanol-glacial acetic acid-water as a solvent system. (Fig. 6.) The fast component had the same Rf value as the bromsulphalein used for injection. The Rf value of the slow components was about half that of the fast component.

In normal subjects all bromsulphalein was excreted in the urine during the first two hours after injection, but in patients with Dubin-Sprinz disease there was still some excretion of bromsulphalein in the urine after forty-eight hours. The total amount of bromsulphalein excreted in the urine in four normal subjects was in the range of 1 per cent to 1.3 per cent (mean 1.2 per cent) of the injected dose. In the patients with Dubin-Sprinz disease this varied from 1.7 per cent to 10.6 per cent (mean 4.8 per cent). The average excretion of the fast component was 0.4 per cent of the injected dose in normal subjects. In patients with Dubin-Sprinz disease about the same amount of the fast component was excreted. However, the amount of the

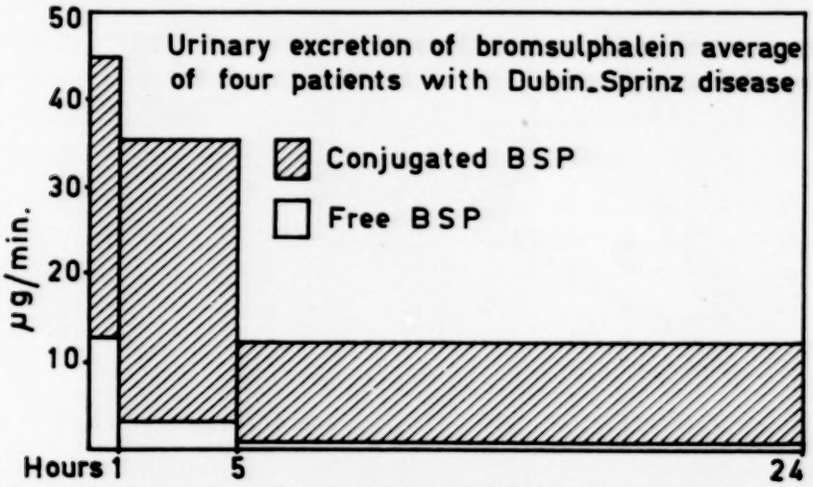


FIG. 9. Urinary excretion of bromsulphalein in Dubin-Sprinz disease. (Mean of Cases I, II, IV and V; in Case III the urine was sampled during other periods.)

slow fractions excreted in the urine of patients with Dubin-Sprinz disease was much greater than in healthy subjects. (Figs. 7, 8, 9 and Table II.)

The fast component appears to be free bromsulphalein excreted by the kidney during the period in which bromsulphalein has not yet been taken up by the liver and is still circulating in the blood. Our data on the excretion pattern of bromsulphalein in the urine of patients with Dubrin-Sprinz disease indicate again that in this disorder there is, at first, a nearly normal uptake of bromsulphalein by the liver but, subsequently, conjugated bromsulphalein re-enters the bloodstream and is partly excreted by the kidneys. After forty-eight hours a trace of conjugated bromsulphalein can still be detected in the urine of patients with Dubin-Sprinz disease. However, only a fraction of the injected bromsulphalein is recovered in the urine, and apart from this amount, most of the bromsulphalein is probably excreted with the bile.

Chromatography of Bromsulphalein in Bile. The same bromsulphalein components found in the urine can be detected in the bile. The slow components in bile are divided more clearly into two fractions than in the urine. In normal subjects the bromsulphalein in the bile obtained by duodenal drainage during the first ninety minutes after intravenous injections of 5 mg./kg. bromsulphalein consists of about 60 per cent free bromsulphalein and about 40 per cent conjugated bromsulphalein.

In patients with Dubin-Sprinz disease the bile collected over the same period contains bromsulphalein almost entirely in the free state, while only traces of conjugated bromsulphalein are found. We think it is possible that the amount of conjugated bromsulphalein increases later on, but unfortunately, at the time of these bile collection experiments we were not aware of the potential importance of collecting the bile over a longer period.

TABLE II

TWENTY-FOUR HOUR URINARY EXCRETION OF BROMSULPHALEIN IN FOUR NORMAL SUBJECTS AND IN FIVE PATIENTS WITH DUBIN-SPRINZ DISEASE, AS PERCENTAGE OF THE DOSE GIVEN

Name	Amount Injected	Total Urinary Excretion	Excretion of Free Bromsulphalein	Excretion of Conjugated Bromsulphalein
Normal Subjects				
S.	355	1.2	0.4	0.8
I.	355	1.0	0.3	0.7
M.	400	1.3	0.5	0.6
F.	400	1.1	0.5	0.8
Mean.....	378	1.2	0.4	0.8
Patients with Dubin-Sprinz Disease				
D. B.	400	2.8	0.4	2.4
P. B.	379	1.7	0.5	1.2
G. B.	445	2.9	0.3	2.6
S. B.	460	10.6	0.6	10.0
H. S.	460	6.2	0.5	5.7
Mean.....	429	4.8	0.5	4.3

The concentration of bromsulphalein in the bile in the patients with Dubin-Sprinz disease was much lower than in normal subjects, but these figures are not very reliable when the bile is collected by means of duodenal drainage. However, it is possible that in Dubin-Sprinz disease the excretion of free bromsulphalein is also impaired to a lesser extent.

In summarizing these findings on bromsulphalein metabolism in Dubin-Sprinz disease, the following tentative conclusions can be drawn: (1) The uptake of bromsulphalein by the liver during the first period after the injection is apparently unchanged. (2) Bromsulphalein is conjugated in Dubin-Sprinz disease as it is in normal subjects. (However a defect of the bromsulphalein conjugating mechanism of the liver has not definitely been ruled out. If such a defect were present, an abnormal uptake by the liver during the first period after the injection might be expected.) (3) The excretion of conjugated bromsulphalein into the bile is markedly delayed in Dubin-Sprinz disease in comparison with normal subjects. (4) This causes entry of an excess of conjugated bromsulphalein from the liver into the blood and increased excretion of conjugated bromsulphalein by the kidneys into the urine.

SUMMARY

This paper deals with five cases of chronic idiopathic jaundice (Dubin-Sprinz disease); four patients were siblings. In two patients concomitant cholelithiasis was observed. In two patients without cholelithiasis, the gallbladder could be well visualized after intravenous contrast dye was given, but only after a delay of five hours.

Biliary excretion of conjugated bromsulphalein is impaired in Dubin-Sprinz disease. This results in re-entry of some of the conjugated bromsulphalein from the liver cells into the blood stream and excretion of an excess of conjugated bromsulphalein by the kidneys.

These abnormalities in bromsulphalein metabolism, together with a familial occurrence, may be useful in establishing the correct diagnosis.

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Roentgenographic Determination of Total Lung Capacity*

A New Method Evaluated in Health, Emphysema and Congestive Heart Failure

HOWARD J. BARNHARD, M.D.,† JOHN A. PIERCE, M.D., JOHN W. JOYCE *and* JOSEPH H. BATES, M.D.

Little Rock, Arkansas

THE determination of total lung capacity has a place in clinical medicine. Its usefulness in the past has been limited by the technical requirements for the measurement of the residual volume. A method for the determination of total lung capacity which does not require special training and equipment could be useful clinically, provided it has sufficient accuracy.

The purpose of the present study was to improve the roentgenographic estimate of total lung capacity (TLC) through a more detailed consideration of the shape of the lungs. The method to be presented is simple and practical. Only the standard 6-foot posteroanterior and lateral chest roentgenograms are required. The measurements and the calculations can be completed within twenty to thirty minutes. The accuracy of this method appears satisfactory for clinical use.

Previous Roentgenologic Methods. The first concerted effort to determine the volume of gas in the lungs from the chest roentgenogram was reported by Hurtado and Fray in 1933 [*1*]. They measured the area of the chest with a planimeter and multiplied this area by the anteroposterior diameter of the thorax as determined externally. As can be seen by reference to Figure 1, the gradual anteroposterior narrowing of the upper thorax and the curvature of the rib cage have been neglected. Also, the mediastinal contents contribute a large additional volume. This overage is only partially overcome by neglecting to measure the posterior sulcus which is hidden by the diaphragm. Hence,

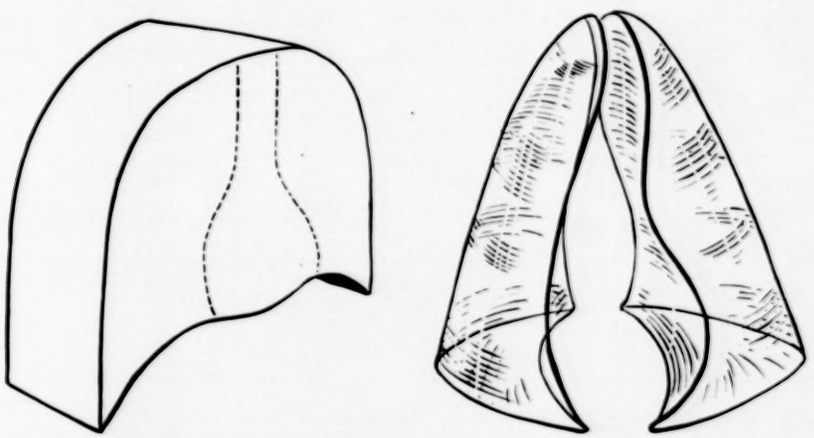


FIG. 1. Representations of the volumes measured by previous roentgenographic methods. *Left*, planimeter method. *Right*, parabola method. The latter was plotted from the roentgenogram shown in Figure 3.

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† Present address: Hahnemann Medical College, Philadelphia, Pennsylvania.

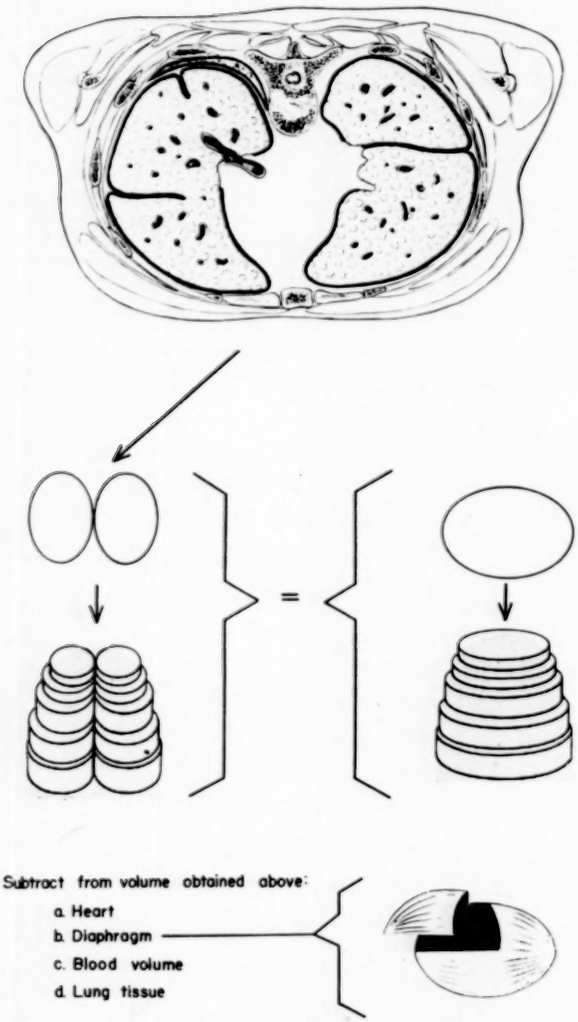


FIG. 2. Rationale of the ellipse method. *Top*, a cross section of the thorax made at the level of the heart illustrates that each lung approximates an ellipse except in the region of the heart. Therefore, if each lung is divided into a series of elliptical cylindroids (*middle left*) the summation of these cylindroids approximates lung volume. Ellipses with common dimensions can be combined (*middle right*). The volumes which must be subtracted are shown at the bottom. The lower right hand figure depicts ⅛ of an ellipsoid which is used to represent each hemidiaphragm. Its curved surface corresponds to the diaphragmatic dome.

the calculated volume is too large. Hurtado and Fray termed this the "radiologic chest volume" and applied an empirical correction obtained from a regression equation. They found a correlation coefficient (r) of 0.64 between the corrected radiologic chest volume and the total lung capacity as determined by a dilution technic.

A number of other investigators [2–6] have used a "planimeter" method. It is difficult to interpret the significance of their results, however, as each new group has calculated correction factors which best fit their data. The reported correlation coefficients have varied from 0.5 to 0.9.

Kovach and associates [7] reported a different approach to the problem in 1956. They used only the posteroanterior roentgenogram and considered the chest as a paraboloid of revolution. A line between the lateral costophrenic sulci established a base line. The distance from this line to the apex determined the chest height. The final shape of the theoretical geometric figure was entirely dependent upon the relationship between the height of the chest and the length of the base line. (Fig. 1.) In general, excessive volume is incorporated in the lower part of the chest while insufficient volume is added superiorly. A balance between these two effects is not assured. These authors subtracted volumes for the heart, diaphragm, and other intrathoracic structures.

Ellipse Method. An examination of the cross sectional anatomy of the thorax (Fig. 2) reveals that each lung is elliptical in shape except in the region of the heart. The long dimension of these ellipses is anteroposterior while their short dimension is transverse. If the chest roentgenogram were divided into an infinitely large number of thin elliptical cross sections, the volume could be obtained readily by integration. This concept forms the basis for the present method. Practical limitations, however, sharply restrict the number of sections which can be used. Hence, relatively large segments are inspected to obtain average diameters, and calculations are made with the assumption that each segment is an elliptical cylindroid.

The area of an ellipse is:

$$\tfrac{1}{4}\pi D_{AP} \times D_T \qquad (1)$$

D_{AP} is the anteroposterior diameter of the ellipse and D_T is the transverse diameter. If the right and left lungs are designated with the subscripts R and L respectively, the lung area in any thoracic cross section then becomes:

$$(\tfrac{1}{4}\pi D_{APR} \times D_{TR}) + (\tfrac{1}{4}\pi D_{APL} \times D_{TL}) \qquad (2)$$

Since $D_{APR} = D_{APL} = D_{AP}$, which is the anteroposterior diameter of the thorax, it can be seen that the summation of two elliptical lung areas at the same level is simplified. Moreover, since $D_{TR} = D_{TL} = \tfrac{1}{2}D_{TT}$, where D_{TT}

is the "total" transverse diameter of the thorax, the final solution for area becomes:

$$\tfrac{1}{4}\pi D_{AP} \times D_{TT} \qquad (3)$$

Expression (3) is identical with expression (1) except that the transverse diameter of the entire thorax is used. Obviously, the volume of an elliptical cylindroid is simply the area of the ellipse multiplied by the height of the cylindroid. Theoretically, then, one may deal with two elliptical figures while mathematically handling only one. This manipulation reduces the number of measurements and calculations to approximately half. Once the volume of these sections is determined, it is necessary to subtract for the volume of the heart, diaphragm, pulmonary blood and lung parenchyma.

The volume of the heart may be calculated as an ellipsoid:

$$\tfrac{4}{3}\pi r_1 r_2 r_3 \qquad (4)$$

Since diameters are more convenient for our purpose this formula became:

$$\frac{4}{3}\pi\frac{d_1}{2}\frac{d_2}{2}\frac{d_3}{2} \quad \text{or} \quad \frac{1}{6}\pi d_1 d_2 d_3 \qquad (5)$$

The diaphragm presents a more formidable problem. No simple geometric shape can meet its varied configuration in all situations. One-eighth of an ellipsoid, however, offers an adequate approximation for each hemidiaphragm. (Fig. 2 *bottom.*) The curved surface represents the diaphragm, and the three flat surfaces are projected anteriorly, inferiorly and medially. Deriving this volume as one-eighth of formula (4) we have:

$$\tfrac{1}{6}\pi r_1 r_2 r_3 \qquad (6)$$

Total blood volume has been related to height by Gibson and Evans [*8*]. Ebert and associates [*9*] found that the intrathoracic blood volume averaged 19.5 per cent of the total blood volume. Arbitrarily, we have assumed that three-fourths of the intrathoracic blood volume is extracardiac. Hence the volume of blood to be subtracted is estimated as 15 per cent of the calculated total blood volume from the data of Gibson and Evans. (Table I.)

Estimation of lung parenchyma volume proved to be another problem. The fibrous connective tissues proteins of the right middle lobe average approximately 1.8 gm. dry weight in adult subjects [*10*]. If we assume that the right middle lobe constitutes 8 per cent of the lungs and further assume that this tissue is 83 per cent hydrated, the calculated volume occupied by the entire lung parenchyma is 132 ml. This quantity has been subtracted in all cases as 130 ml.

TABLE I
THE BLOOD VOLUME OF THE LUNGS AS OBTAINED FROM THE HEIGHT (BY CALCULATION)

	0	1	2	3	4	5	6	7	8	9
Male										
160	672	700	704	733	738	767	771	776	806	811
170	816	821	826	830	835	840	844	850	854	859
180	864	868	873	878	883	888	892	897	902	907
Female										
150	517	521	524	551	554	558	561	565	568	572
160	576	580	583	587	590	594	599	601	605	608
170	612	616	619	622	626	630	634	637	641	644

NOTE: The left column and top row indicate the height in centimeters. Example: A man 185 cm. tall has a lung blood volume of 888 ml.

The Ellipse Method Applied. Posteroanterior and left lateral roentgenograms of the chest are made at a target film distance of 6 feet. It is imperative to obtain maximal inspiratory effort. The patient should be erect as possible and in the same posture for both views but the arms are raised while the lateral view is exposed. The lateral view should be slightly overpenetrated to facilitate accurate measurements in the apical region.

I. Measurements (Fig. 3)
  A. Posteroanterior x-ray film.
    1. Outline the lateral and superior boundaries of the lungs by following the inner rib borders with a wax pencil.
    2. Divide the superior portion of the thorax into two segments with transverse lines 2.75 cm. apart (segments I and II in Figure 3).
    3. Draw a line transversely at the higher dome of the diaphragm.
    4. Divide the large area into two parts with another transverse line (segments III and IV in Figure 3).
  B. Lateral x-ray film.
    1. Outline the lung boundaries as before.
      a. To assure accuracy, first draw the transverse line at the higher dome of the

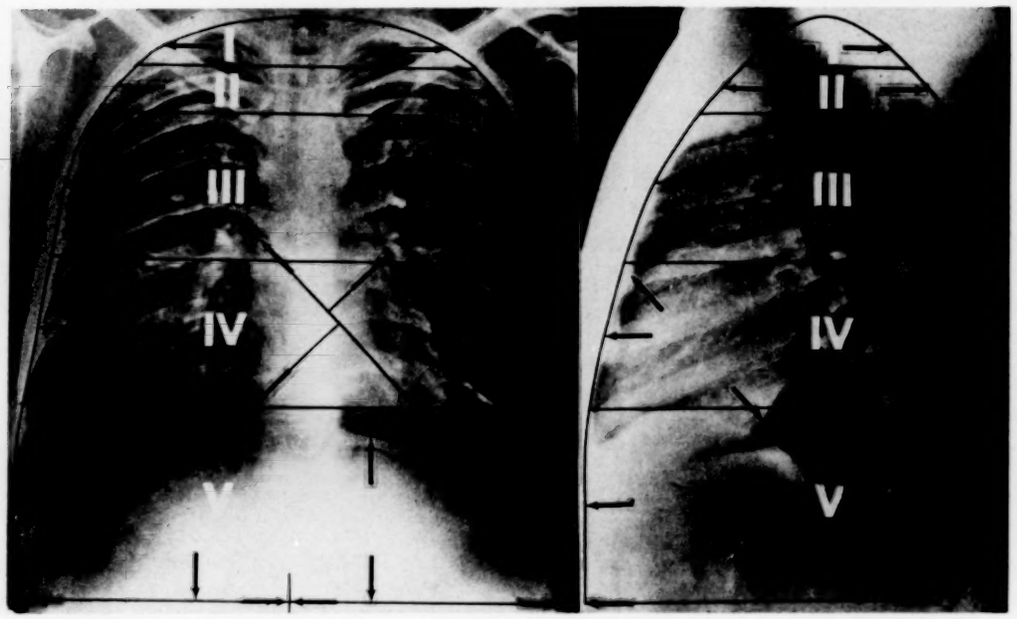


FIG. 3. Roentgenograms prepared for measurement. The arrows indicate the actual points between which to measure.

diaphragm. Then validate the upper limit of the apex by measuring from this line a distance equal to that found on the posteroanterior roentgenogram.

b. If the posterior ribs on opposite sides do not superimpose, draw a line which represents the average between their inner margins.

2. Draw in the same four segments as on the posteroanterior x-ray film.

3. The inferior segment (v on Figure 3) is completed by drawing a line parallel to the others at the level of the posterior sulcus. The anterior line is then extended perpendicularly to meet this base line.

C. Return to the posteroanterior x-ray film.

1. Draw a transverse line which is as far below the line of the diaphragmatic dome as found on the lateral roentgenogram.

2. Extend vertical lines from the lateral costophrenic angles to meet this base line. Note: Occasionally an unusual configuralion of the chest necessitates the use of a targer number of segments. This situation exists when the slope of a boundary line in any segment changes direction or becomes more or less abrupt. Then the mid-plane of that segment no longer represents an "average" cross section, and the segment must be further divided.

II. Calculations (Fig. 4)

A. Subtract 10 per cent from all measurements for the divergence of the x-ray beam.

B. Determine the volume of each elliptical cylindroid with the formula: $V = \frac{1}{4}\pi \times$ transverse diameter $\times$ AP diameter $\times$ height of the segment.

C. Add the volumes obtained from the five or more segments.

D. From this volume subtract the following:

1. Heart—on the posteroanterior roentgenogram establish the long diameter (d_1) by drawing the longest possible line from the junction of the superior venous pedicle with the right atrium to the left heart border, usually as it meets the diaphragm. From this line extend perpendiculars to the furthest point of the left and right heart borders. The sum of these two perpendiculars is used as the second diameter (d_2). On the lateral view draw the longest possible line (d_3) roughly perpendicular to the long diameter. Calculate as: $V = \frac{1}{6}\pi d_1 \times d_2 \times d_3$.

2. Diaphragm—each hemidiaphragm is calculated separately. The base line on the posteroanterior x-ray film is divided into two equal parts, each half being r_1. The distance from the base line to each diaphragmatic dome is r_2. The length of

Thoracic Segment	Diameter (PA film)	Diameter (Lat film)	Height	Volume
I	13.5	7.0	2.5	185
II	19.3	11.7	2.5	474
III	24.0	17.1	7.5	2420
IV	27.0	21.1	7.5	3355
V	28.8	20.4	10.3	4760
(VI)	____	____	____	

Total Thoracic Volume 11,194

Dome of Diaphragm	Radius (PA film)	Radius (Lat film)	Height	Volume
Right	14.1	18.8	10.3	1430
Left	14.1	18.8	8.6	1192

Heart	Long Axis (PA film)	Transverse Axis (PA film)	Depth (Lat film)	
	15.0	10.0	9.9	778
Lung Tissue				130
Blood derive from height-blood volume table				888

Volume to be subtracted 4,418

TOTAL LUNG CAPACITY 6,776 ml.

FIG. 4. A form showing the measurements and results from the case in Figure 3.

the base line on the lateral view is r_3. Calculate as $V = \frac{\pi}{6} r_1 r_2 r_3$.

3. Blood volume—see Table 1.
4. Lung parenchyma volume—use value of 130 cc.

Physiologic Methods. All spirometric and residual volume determinations were performed with the subjects sitting upright. Residual volume determinations were performed twice using an open circuit nitrogen dilution technic. The methods and the tolerance in these measurements and in the blood gas analyses were essentially the same as those in a previous report [*11*]. This determination of TLC combines spirometric and nitrogen dilution measurements, and will be referred to subsequently as the "dilution" method.

Subjects. Four groups of subjects were studied: healthy young subjects, healthy old subjects, patients with emphysema, and patients with congestive heart failure. Insofar as possible the roentgenograms of the chest were obtained on the same day that the pulmonary function studies were performed. Subjects with asthma, pneumothorax, pleural effusion, masses or localized areas of pulmonary consolidation were not included in this study.

The healthy young subjects were medical students and members of the staff. Their ages ranged from twenty-two to thirty-seven years. None had symptoms of respiratory infection at the time of the study.

The healthy old subjects were patients under treatment for non-pulmonary diseases. Their ages ranged from fifty-five to ninety-two years. These patients did not have respiratory symptoms, and pulmonary function studies were considered normal for subjects of their age.

The patients with emphysema were thought

TABLE II

PHYSICAL CHARACTERISTICS AND LUNG FUNCTION STUDIES

Group		Age (yr.)	Body Surface Area (sq. m.)	Total Lung Capacity (L.)	Vital Capacity (L.)	Ratio RV/TLC* (%)	Functional Residual Capacity (L.)	Index of Mixing† (%)	Maximum Breathing Capacity (L./min.)	Arterial Blood pCO_2 (mm. Hg)	Arterial Oxygen Saturation (%)
Healthy young subjects N-21	Mean....	28	1.92	7.02	5.51	21.0	3.79	0.55	138‡	.....	.....
	S. D. ...	5	0.12	1.17	0.78	3.3	0.76	0.36	29	.....	.....
	Range...	23–37	1.65–2.14	5.64–9.74	4.60–7.16	15.5–26.5	2.16–4.92	0.14–1.94	71–205	.....	.....
Healthy old subjects N-25	Mean....	72	1.79	6.54	3.81	42.3	4.37	1.37	70‖	37‖	93‖
	S. D.....	9	0.16	1.21	1.16	8.3	0.81	0.68	21	7	3
	Range...	55–92	1.53–2.17	4.13–9.29	1.96–5.50	28.4–59.2	2.56–5.75	0.37–2.93	40–118	28–51	83–97
Patients with emphysema N-16	Mean....	63	1.71	6.46	2.91	54.9	4.84	7.02	33	49¶	87
	S. D.....	11	0.16	0.79	0.51	6.0	0.70	3.02	13	12	7
	Range...	47–85	1.44–2.07	5.59–7.57	2.20–3.97	40.9–63.1	3.97–6.06	1.53–12.90	15–61	35–72	75–97
Patients with congestive heart failure N-12	Mean....	55	1.77	4.03	2.26	42.8	2.49	1.06	45**	34††	91**
	S. D.....	21	0.23	0.35	0.53	9.4	0.78	0.47	17	7	3
	Range...	20–85	1.53–2.29	2.62–6.00	1.50–3.27	22.2–53.8	1.52–4.07	0.39–2.49	11–67	25–47	87–96

* Residual volume to total lung capacity.
† Nitrogen concentration of alveolar gas after seven minutes breathing pure oxygen.
‡ n = eighteen subjects.
§ Standard deviation.
‖ n = twenty-four subjects.
¶ n = fifteen subjects.
** n = eleven subjects.
†† n = ten subjects.

TABLE III

TOTAL LUNG CAPACITY OF INDIVIDUAL SUBJECTS

Subject No.	Healthy Young Group			Healthy Old Group			Emphysema Group			Congestive Heart Failure Group		
	B.S.A.*	Spirometric T.L.C.†	X-ray Film T.L.C.	B.S.A.	Spirometric T.L.C.	X-ray Film T.L.C.	B.S.A.	Spirometric T.L.C.	X-ray Film T.L.C.	B.S.A.	Spirometric T.L.C.	X-ray Film T.L.C.
1	2.11	9.74	8.74	1.53	4.43	4.48	1.74	7.57	7.89	1.80	5.49	4.96
2	1.95	7.76	6.87	1.69	7.83	7.71	1.90	7.57	7.16	2.14	6.00	7.09
3	1.65	6.95	6.46	1.97	7.56	8.59	1.91	6.72	7.61	1.64	2.85	3.15
4	2.08	9.24	9.00	1.84	6.37	7.41	1.58	5.65	7.32	1.53	2.97	3.41
5	1.88	5.69	5.47	1.87	5.33	5.81	1.60	6.45	6.76	1.81	3.77	4.39
6	2.08	8.69	9.11	1.79	7.45	7.30	1.85	5.86	6.57	1.68	3.25	3.80
7	1.87	6.48	6.60	1.72	5.31	5.53	1.61	6.33	6.34	1.62	2.62	3.46
8	1.80	6.71	5.49	1.81	6.64	5.95	1.62	4.95	5.66	1.64	3.70	3.05
9	1.96	7.05	6.81	1.68	6.42	5.90	1.53	7.26	7.53	1.76	4.35	3.64
10	1.88	6.42	7.00	1.74	6.30	5.56	1.66	6.21	7.53	1.78	3.54	3.57
11	1.82	6.25	5.69	1.82	5.88	6.20	1.62	6.95	8.05	1.56	4.68	4.56
12	1.80	6.79	7.15	1.69	5.99	5.41	1.67	7.47	7.91	2.29	5.18	5.52
13	1.91	5.64	5.56	2.17	7.31	8.35	2.07	5.59	8.17	....	....	....
14	1.90	8.19	7.48	1.83	6.19	5.88	1.70	6.33	8.60	....	....	....
15	1.93	6.48	5.83	1.74	6.79	6.33	1.80	5.65	6.85	....	....	....
16	1.99	7.62	7.75	1.81	7.26	6.94	1.44	6.82	6.40	....	....	....
17	1.84	5.93	6.73	2.08	7.30	8.28	....	....	....	....	....	....
18	1.84	7.10	6.31	1.76	7.64	6.67	....	....	....	....	....	....
19	1.80	5.75	5.30	1.56	6.53	5.93	....	....	....	..	....	....
20	2.14	7.19	6.78	1.54	6.60	6.96	....	....	....	....	....	....
21	2.05	5.76	6.16	1.98	9.29	9.51	....	....	....	....	....	....
22	....	....	....	1.99	8.02	8.45	....	....	....	....	....	....
23	....	....	....	1.61	6.51	6.96	....	....	....	....	....	....
24	....	....	....	1.64	4.38	4.47	....	....	....	....	....	....
25	....	....	....	1.87	4.13	5.25	....	....	....	....	....	....
Mean..	1.92	7.02	6.78	1.79	6.54	6.63	1.71	6.46	7.27	1.77	4.03	4.22

* Body surface area in square meters.
† Total lung capacity in liters.

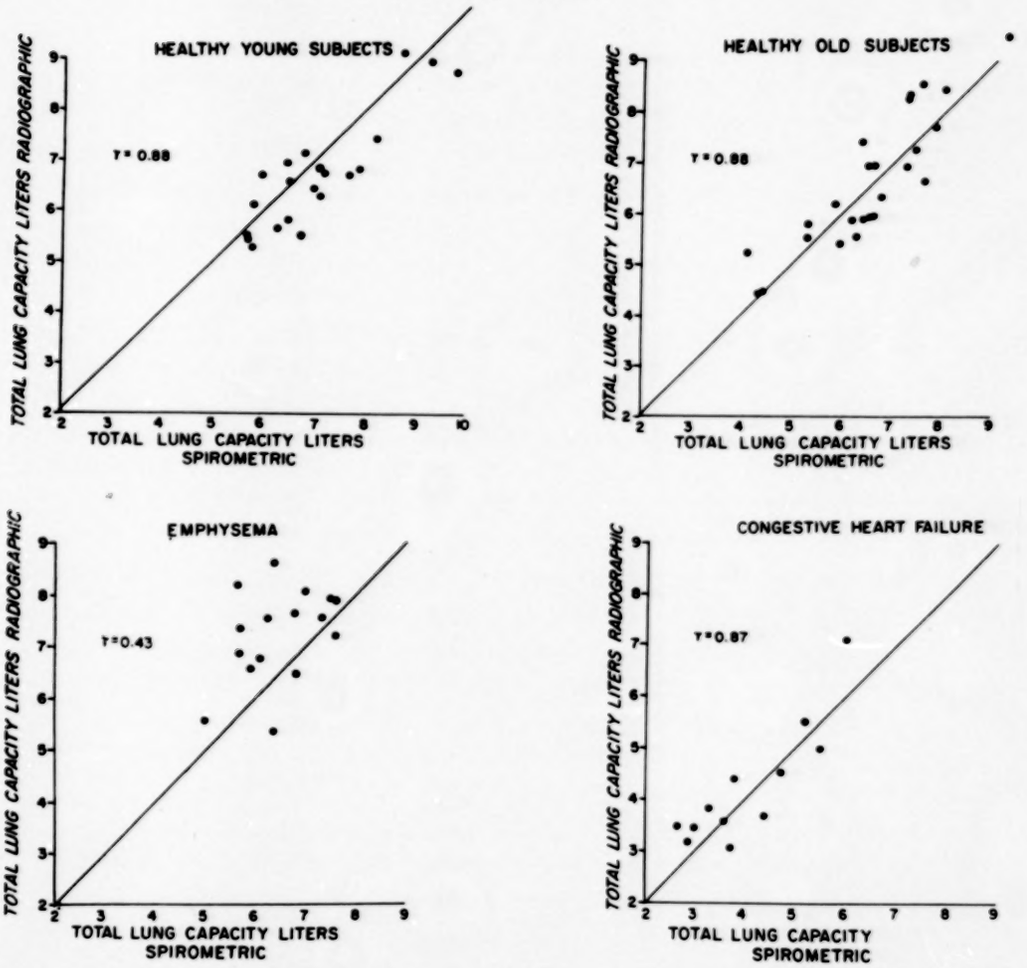


FIG. 5. Dilution measurements of total lung capacity plotted against the roentgenographic ellipse measurements in each group. In this Figure and in Figures 6 and 7 the diagonal line in each graph does not represent a calculated regression line but is a line of ideal agreement

to have pulmonary emphysema as evaluated clinically. In addition, physiologic studies revealed marked abnormalities in the rate of expiratory air flow and in the alveolar nitrogen concentration after seven minutes of breathing pure oxygen. The ratio of residual volume to total lung capacity tended to be high. The carbon dioxide tension of arterial blood was elevated in approximately half of the patients. The ages in this group ranged from forty-seven to eighty-four years.

The patients with congestive heart failure had the usual clinical findings of this condition including marked cardiac enlargement, pedal edema, elevated venous pressure and prolonged arm to tongue circulation time. In general, these patients were very ill. The etiology of their heart disease was quite varied. Because of the rapid improvement which frequently occurs following hospitalization in such patients, the physiological studies and the roentgenograms were completed shortly after admission. These subjects had the widest age range, from twenty to eighty-five years.

RESULTS

All four groups of subjects were studied by the "ellipse" method. In addition, twenty subjects from the healthy young group were evaluated both by the planimeter method of Cobb [*6*] and the "parabola" method of Kovach [*7*].

The mean results of the physiologic studies for each group are shown in Table II. The individual values for total lung capacity (TLC) as determined by the dilution method and by the ellipse method from the roentgenograms are presented in Table III. The TLC was markedly reduced in the subjects with congestive heart failure.

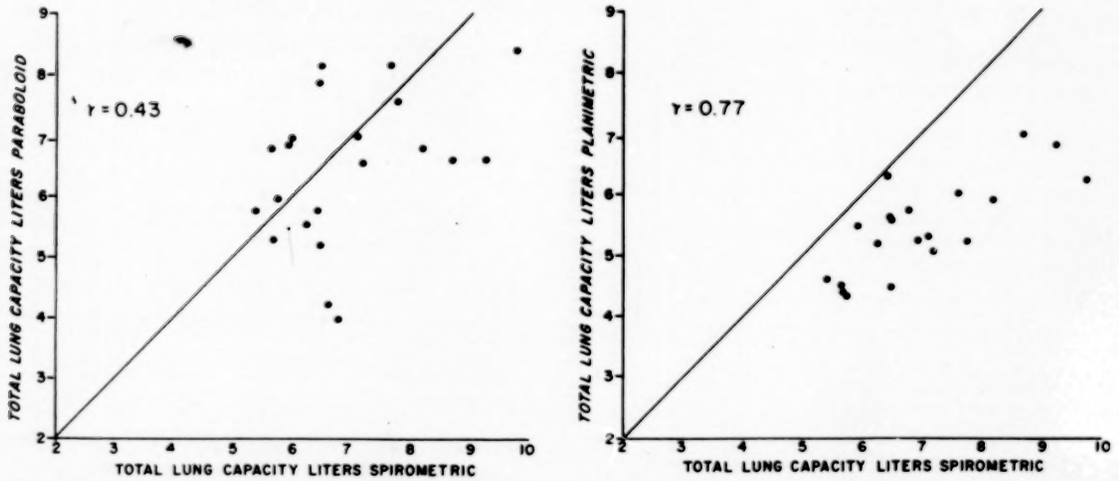


FIG. 6. Comparative studies of the parabola method (*left*) and planimeter method (*right*) in the group of healthy young subjects. See also upper left graph in Figure 5.

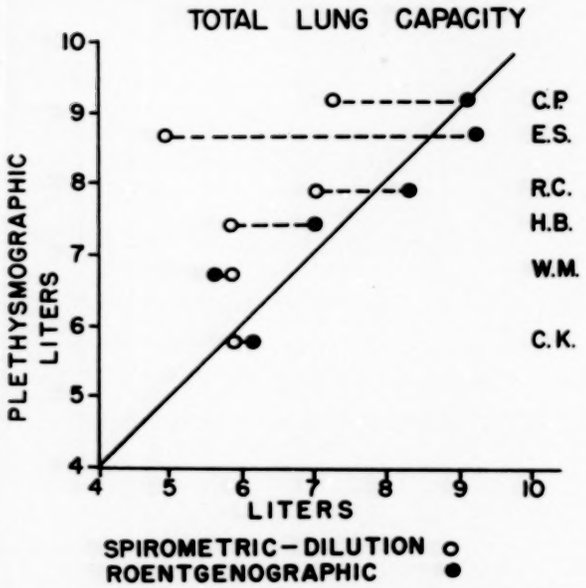


FIG. 7. Data of Bedell and associates [*13*] in six patients with emphysema comparing the dilution and the present ellipse roentgenographic method plotted against the plethysmographic findings. The initials at the right identify the subjects in their paper.

There was no significant difference in the mean TLC of the emphysematous group as compared to the healthy groups when measured with the dilution method. A significant difference does exist however in the TLC of the emphysema group when the results of dilution measurements are compared to the roentgenographic method.

Figure 5 plots the dilution measurements of TLC against the roentgenographically determined TLC when the present method was employed. A high degree of correlation exists between these methods in all except the group of subjects with emphysema. It should be emphasized that the diagonal line shown in each graph does not represent a calculated regression line but is a line of ideal agreement.

Figure 6 presents data on the twenty healthy young subjects as measured by the other roentgenographic methods. These results are plotted against TLC as determined by the dilution method. A poor correlation ($r = 0.43$) was found with the method of Kovach. There was better correlation ($r = 0.77$) with measurements by the planimetric technic.

It was determined in six healthy young subjects that elevation of the arms did not significantly affect the roentgenographic TLC. This indicates that an error is not introduced by taking the posteroanterior roentgenograms with the arms at the sides and lateral roentgenograms with the arms overhead.

Roentgenograms were obtained* of patients with emphysema who had been studied at another center with a plethysmographic technic. The plethysmographic method is superior to the nitrogen dilution technic in instances when some intrathoracic gas is either not in communication with the tracheobronchial tree, or communicates with it only periodically. In six patients whose roentgenograms were suitable for measurement there was a much better correlation between the plethysmographic and the roentgenographic measurements of TLC than between either of these measurements and the

* Through the courtesy of Dr. A. B. DuBois, Philadelphia, Pennsylvania.

values obtained by the dilution method. Although this series is small, the data have been plotted in Figure 7.

COMMENTS

Roentgenographic measurements of total lung capacity (TLC) start with the same crude data, the posteroanterior view with or without the lateral chest roentgenogram. The manner in which these data are used differs with the method. The present method recognizes the elliptical shape of the lungs and uses the diameters of several lung segments. The results presented for healthy persons and for patients with congestive failure are in agreement with measurements of TLC by a standard spirometric nitrogen dilution method. Inasmuch as the dilution technic is known to measure accurately the residual volume in healthy persons, it may be concluded that the present roentgenographic method affords a reliable estimate of TLC.

The group of patients with congestive heart failure were of interest because of their markedly reduced total lung capacity. It has been known for several years that dilution measurements give a reproducible estimate of the residual volume in such patients [*12*]. The roentgenographic correction applied for the heart volume and pulmonary blood volume in these patients was identical with that used in the other groups. The high correlation between roentgenographic and dilution measurements of total lung capacity suggests that during congestive heart failure not only is the amount of air in the lungs diminished, but the total volume occupied by the lungs is also reduced. Thus, the decrease in total lung capacity in congestive heart failure is not due primarily to an excessive volume of either blood or edematous fluid in the lungs.

Patients with obstructive pulmonary emphysema were found to have a significantly greater TLC by the roentgenographic method than by the spirometric nitrogen dilution technic. In order to determine whether this discrepancy was due to an alteration in the shape of the chest in the subjects with emphysema, we studied a group of subjects who had a marked barrel deformity of the chest but who did not have emphysema. Correlation between roentgenographic and dilution measurements of TLC was found to be identical with that found in healthy young subjects. It was concluded therefore that marked rounding of the chest, as occurs with the barrel deformity, does not in itself interfere with the determinations of TLC by the present roentgenographic method.

In connection with emphysema, the work of Bedell, Marshall, DuBois and Comroe [*13*] is important. They measured intrathoracic gas with a body plethysmograph. In eleven patients with pulmonary emphysema, they found that the mean TLC was greater by 1.09 L. when determined in the plethysmograph than with the spirometric nitrogen dilution technic. This value agrees with the mean difference of 0.8 L. in the present study of seventeen patients with emphysema. This discrepancy occurred in the measurement of the residual volume because the lung nitrogen was inadequately diluted during the seven-minute test period of oxygen breathing. Most important among the factors which contributed to this inadequate dilution was the markedly abnormal distribution of inspired gas and the phenomenon of gas trapping. Both of these factors characteristically occur in patients with severe emphysema. The roentgenographic method was found to correlate well with plethysmographic determinations in the six patients which were compared. This finding tends to validate the roentgenographic method for measuring TLC in patients with emphysema.

It has been repeatedly shown that patients with pulmonary emphysema have an increased residual volume, an increased functional residual capacity and a reduced vital capacity as compared to healthy persons. These patients also exhibit a markedly increased resistance to expiratory air flow. Diagrams of the lungs which relate pressure to volume show a smaller transpulmonary pressure at every level of lung inflation in emphysema than is found in healthy young subjects. This change in the volume elastic properties of the lungs is similar to the alterations found in healthy aged persons.

In the present group of emphysematous patients it was found that when residual volume was estimated as the difference between the roentgenographic TLC and the vital capacity, the mean ratio of residual volume to total lung capacity rose from 55 to 60 per cent. This change was significant statistically ($P = 0.02$). When similar calculations were made for the group of healthy old subjects, the ratio remained at 43 per cent. It is obvious then that a better differentiation between emphysematous and healthy aged subjects occurs when the ratio of residual volume to total lung capacity is cal-

culated with the roentgenographic than with the dilution method for measuring TLC.

The significance of the finding that patients with pulmonary emphysema have approximately 1 L. of gas in their lungs over that shown by the nitrogen dilution method must be emphasized. It means that pressure volume diagrams of the lungs which have been calculated on the basis of dilution measurements actually show erroneously small volumes in emphysema. Hence, alterations in the volume elastic properties of the lungs in emphysema are more severe than has been indicated previously.

SUMMARY

1. A roentgenographic method for the determination of total lung capacity has been described. This method requires posteroanterior and lateral views of the chest and principally involves the summation of a series of elliptical cylindroids into which the lungs are divided. The method is simple, rapid and accurate.

2. The roentgenographic method was compared to a conventional physiologic measurement of total lung capacity in seventy-four persons. A high degree of correlation was found in healthy young subjects, healthy old subjects, and patients with congestive heart failure. A significantly lower correlation was found in patients with emphysema.

3. The mean total lung capacity in the emphysema group was 0.81 L. more by the roentgenographic method than by the dilution technic. This discrepancy appears to result from errors in the measurement of the residual volume by the nitrogen dilution method. It illustrates further that there is a more severe alteration of the volume elastic properties of the lungs in emphysema than was previously indicated.

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Physiologic Dead Space in the Hamman-Rich Syndrome*

Physiologic and Clinical Implications

ROBERT A. B. HOLLAND, M.B., M.R.A.C.P.

Sydney, New South Wales

SINCE Hamman and Rich [*1*] described four cases of the diffuse interstitial pulmonary fibrosis which bears their name, many cases have been reported. However, in only a few have extensive physiologic studies been made. The thickened alveolar walls give rise to difficulty in gas diffusion with arterial oxygen unsaturation in severe cases. Several reports of this aspect have appeared [*2–6*], but in none have the values for dead space been reported. Similarly, in several series of mixed types of pulmonary fibrosis and granulomatoses [*3,7–9*] dead space was not estimated. Austrian et al. [*10*] and Donald et al. [*11*] have found a high dead space in subjects at rest, particularly in those with more severe fibrosis. In the following paper, the values of physiologic dead space estimated at rest and on exercise in five subjects with Hamman-Rich syndrome are presented. The effect of dead space values on the symptomatology is considered, as well as its implications regarding the validity of certain methods of measuring pulmonary diffusing capacity.

METHODS

Physiologic dead space was calculated for carbon dioxide from the Bohr equation, using arterial carbon dioxide tension, and regarding inspired carbon dioxide tension as zero (breathing air).

$$\text{Thus: } \frac{\text{dead space}}{\text{tidal volume}} = \frac{\text{arterial } CO_2 \text{ tension} - \text{expired } CO_2 \text{ tension}}{\text{expired } CO_2 \text{ tension}}$$

The subjects were studied breathing on an open circuit into a Douglas bag. Resting studies were performed on a cardiac bed sitting at an angle of 70 to 80 degrees. Exercise was performed on a stationary ergometer bicycle. Five minutes was allowed at any level of exercise for a steady state to be reached.

Expired air was analysed for carbon dioxide on the Haldane apparatus, duplicates being required to check to within 0.02 per cent. Arterial blood was obtained throughout the collection period from a needle indwelling in the brachial artery. Determinations of blood gas content were performed by the methods of Van Slyke and Neill [*12*]. The pH of whole blood was determined in an anerobic cell with a Stadie microelectrode and a Cambridge meter specially calibrated to read to .005 pH units by the National Standards Laboratory. It was measured at the temperature of running water and corrected to 37°C. by the formula of Rosenthal [*13*]. Arterial carbon dioxide tension was obtained by the nomogram of Singer and Hastings [*14*], correcting for oxygen unsaturation when necessary. Measurements were made at sea level; the dead space is expressed at body temperature and ambient pressure saturated with water vapour.

The mouthpiece was T-shaped with spearpoint valves. Its internal volume was approximately 70 ml. in the earlier studies and approximately 60 ml. in the later ones, but the nature of a spearpoint valve system makes its volume hard to estimate. It is believed that in all cases the volumes used for the apparatus dead space are too high, resulting in a slight underestimation of the dead space in the individual.

RESULTS

Clinical data of the five cases studied are shown in Table 1.

All the patients had the history, physical signs and radiologic picture of pulmonary fibrosis of the Hamman-Rich type. There was no suggestion of a definite cause for the fibrosis in the history, physical examination or special investigations. In four cases, histopathology confirmed the diagnosis. In one subject (R. F.), the diagnosis rested on clinical and radiologic evidence and a negative scalene node biopsy.

All patients showed an increase in physiologic

* From the Department of Medicine, University of Sydney, Sydney, New South Wales. Supported in part by the National Health and Medical Research Council and by the Joint Coal Board.

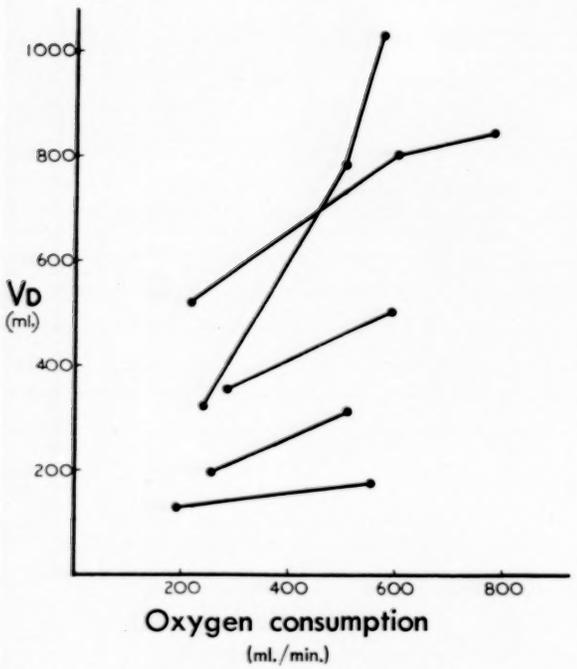


FIG. 1. The physiologic dead space (corrected for mouthpiece) and its increase with exercise.

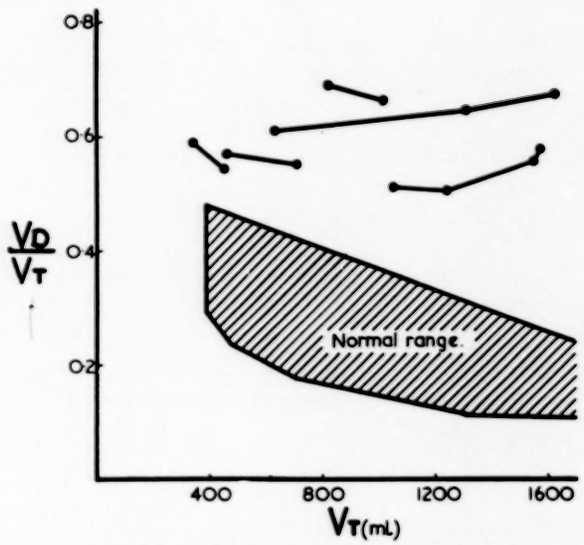


FIG. 2. The effect of change of tidal volume on ratio of dead space (uncorrected for mouthpiece) to tidal volume. All values of normal subjects fell within the shaded area.

dead space at rest (Table II and Fig. 1) and in two subjects (W. J. and D. C.) it was marked. Two subjects (S. K. and R. F.) showed no increase in absolute figures for the corrected dead space, but the ratio of corrected dead space to tidal volume was much increased, particularly when it is remembered that at their relatively low tidal volumes, 70 ml. was almost certainly too much to allow in correcting for apparatus dead space. In a study of normal subjects in this laboratory [*15*] twenty-one men at rest had a mean corrected physiologic dead space of 133 ml., the range being 216 to 81 ml. For women, the mean was 94 ml., the range being 121 to 40 ml. The ratio of corrected dead space to tidal volume was 0.35 to 0.15 with a mean of 0.23. The low values were doubtlessly false due to correction by subtraction of the full value of the mouthpiece volume in persons with low tidal volumes. These figures are in accord with those of other workers. It is seen that all patients with the Hamman-Rich syndrome had a resting dead space/tidal volume ratio higher than normal, and all but one (R. F.) had a dead space greater than any of the normal subjects of corresponding sex.

TABLE I
DATA OF SUBJECTS STUDIED

Subject	Sex	Age (yr.)	Height (in.)	Weight (lb.)	Body Surface Area (M^2)	Degree of Disability	Method of Diagnosis
W. J.	M	54	68	132.5	1.71	Severe	Lung biopsy and autopsy
D. C.	M	32	71	121	1.72	Moderate	Lung biopsy
S. K.	F	17	60	88	1.31	Moderate	Lung biopsy and autopsy
R. F.	M	61	65.5	121	1.60	Mild	Clinical and radiologic
W. S.	M	57	65	153	1.76	Severe	Lung biopsy

On exercise, the dead space showed a marked increase in all subjects. (Table II and Fig. 1.) None of the patients was able to do more than light exercise, but large values for the dead space were reached in some cases. In Figure 2 the ratio of dead space (uncorrected for mouthpiece) to tidal volume is plotted against tidal volume. This demonstrates that in any individual there is little change in this ratio as the tidal volume increases with exercise or with change in ventilatory pattern. In normal subjects the physiologic dead space showed little increase with exercise or hyperventilation, while the ratio V_D/V_T fell as tidal volume increased. All the values of the dead space/tidal volume ratio (uncorrected for the mouthpiece) in normal subjects (resting, exercising or hyperventilating) fell within the shaded area of the figure.

In Figures 1 and 2, most of the duplicate and repeat estimations have been omitted for the sake

TABLE II

THE DEAD SPACE AND DEAD SPACE/TIDAL VOLUME RATIO IN THE PATIENTS STUDIED. ALL ESTIMATIONS ARE SHOWN. IN THE RIGHT HAND COLUMN IS SHOWN THE DEAD SPACE, RECALCULATED TO ALLOW FOR SOME VENOUS ADMIXTURE

Subject	O_2 Uptake (ml./min. STPD)	Tidal Volume (ml. BTPS)	CO_2 Tension (mm. Hg)		Dead Space/Tidal Volume Ratio		Physiologic Dead Space (ml. BTPS) Corrected for Mouthpiece	Physiologic Dead Space (ml. BTPS) Based on Arterial CO_2 Tension—3 mm. Hg
			Expired Air	Arterial Blood	Uncorrected for Mouthpiece	Corrected* for Mouthpiece		
W. J.	292	694	14.0	39.7	0.65	0.61	382	360
	302	835	12.7	38.0	0.67	0.64	489	462
	277	679	12.7	38.2	0.67	0.63	386	364
	281	609	10.8	36.7	0.71	0.67	359	344
	290	625	11.6	36.1	0.68	0.64	354	334
	593	886	12.4	36.5	0.66	0.63	502	476
D. C.	234	1527	17.5	27.6	0.37	0.34	489	371
	271	1349	17.7	27.6	0.36	0.32	413	308
	827	1906	16.6	32.1	0.48	0.46	849	750
	212	1054	15.6	32.4	0.52	0.49	488	434
	221	1234	14.7	29.6	0.50	0.48	561	492
	603	1553	16.0	35.7	0.55	0.53	797	734
	784	1576	14.4	33.7	0.57	0.55	841	777
S. K.	188	334	16.6	41.6	0.60	0.48	131	120
	186	339	16.9	40.4	0.58	0.47	127	116
	552	450	18.8	41.1	0.54	0.46	174	159
R. F.	257	477	18.8	43.1	0.56	0.49	199	183
	250	451	18.3	43.0	0.57	0.50	189	174
	509	700	19.9	43.9	0.55	0.50	312	289
	504	708	20.0	42.7	0.53	0.48	307	281
W. S.	214	599	15.0	32.5	0.54	0.49	262	235
	209	612	14.4	32.5	0.56	0.51	280	253
	443	1095	13.3	31.1	0.57	0.55	559	507
	598	1616	11.3	29.0	0.61	0.59	916	843
	234	627	13.8	35.0	0.61	0.57	320	297
	505	1309	12.9	36.1	0.64	0.63	782	738
	575	1636	11.7	35.0	0.67	0.65	1028	977
	232	513	13.8	34.6	0.60	0.55	249	228
	†	518	13.2	37.4	0.65	0.60	276	259
	†	399	13.1	37.3	0.65	0.59	199	187

NOTE: STPD = standard temperature and pressure (dry).
BTPS = body temperature and pressure (saturated).
* Dead space and tidal volume both corrected for mouthpiece.
† Oxygen consumption not measured. Patient at rest breathing 100 per cent oxygen.

of clarity. In each case the points used were all obtained on the one day, and the same days were used in both graphs.

In three subjects (W. J., D. C. and W. S.), there was much focal emphysema in the lung specimens obtained and examined microscopically at about the time of testing. In one patient (S. K.) although the thickening of alveolar walls was marked in the biopsy specimen, no focal emphysema was present at that time. These changes are shown in Figure 3. In one subject (R. F.) no specimen was available. Thus, the

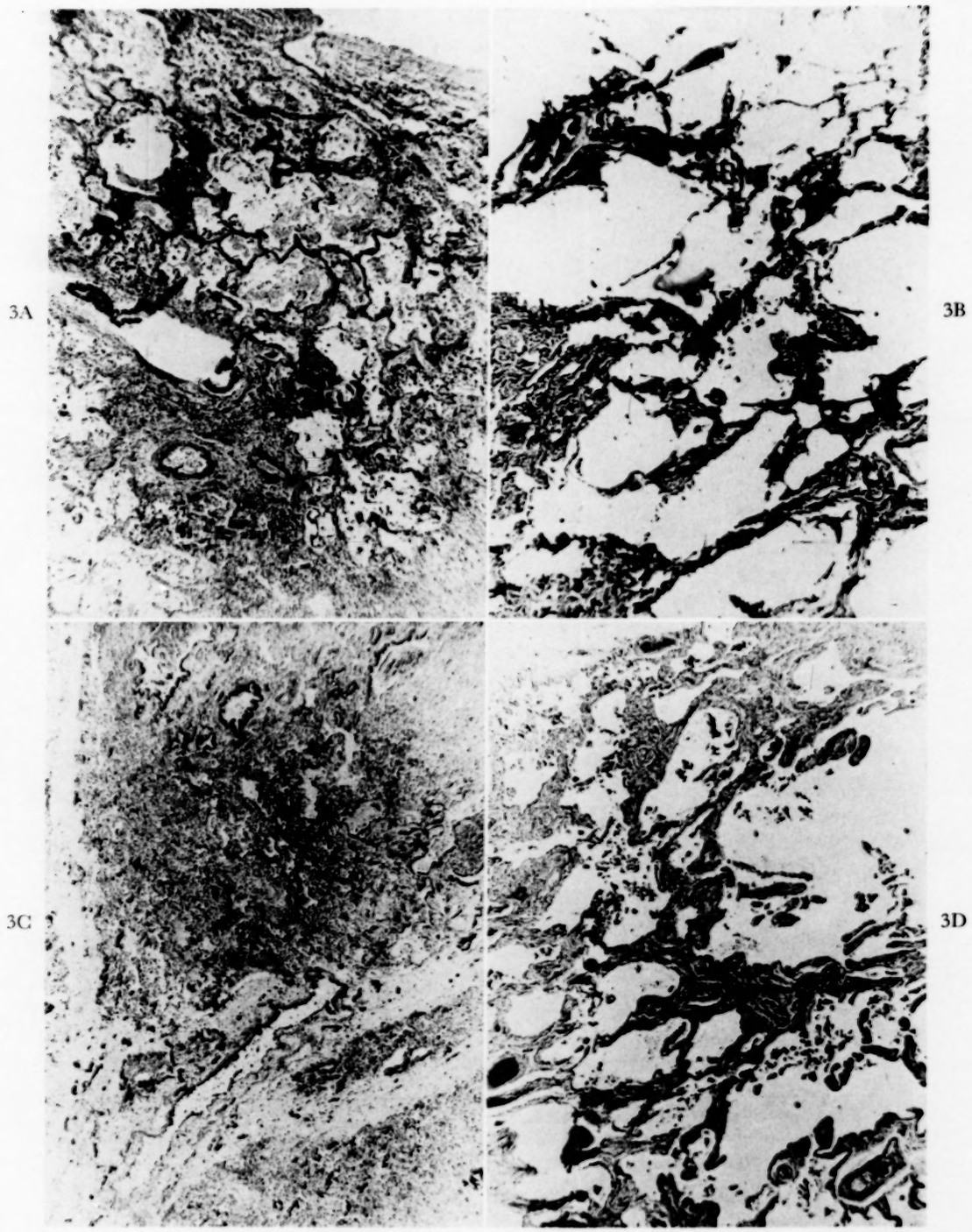


FIG. 3. Photomicrographs of lung specimens. A, subject W. J. B, subject D. C. C, subject S. K. D, subject W. S. Note the emphysematous change in W. J., D. C. and W. S., and its absence in S. K. All specimens were obtained at about the time of testing. A, this section (autopsy) also shows pneumonia. B, this specimen corresponds to the first series of tests in subject D. C., performed sixteen months before the second series.

size of the physiologic dead space correlated well with the amount of emphysema present, and it is to the presence of such unperfused areas in the lung that most of the increase in dead space is attributed.

COMMENTS

The Meaning of Physiologic Dead Space. In abnormal conditions of the lung, the concept of dead space is not as clear as it appears in the normal lung. This is largely because of difficulty in the definition of physiologic dead space. For this reason, a more strict consideration of the problem is necessary.

It is generally accepted that the tidal volume can be divided into two parts, one of which is the physiologic dead space and the other, as designated here, is physiologic alveolar volume. Neither has fixed boundaries and they merge with each other. The size of the dead space is determined, not only by the amount of air whose inspired concentration remains unchanged, but also by quantities of air which do not come into contact with enough blood for their gaseous composition to be changed fully. These contribute to the dead space according to their size and to the degree to which the air remains unaltered.

Since physiologic dead space and physiologic alveolar ventilation are interdependent, neither can be defined in terms of the other. Nor can arbitrary anatomic boundaries be used. Rossier and Bühlmann [*16*] define alveolar ventilation in terms of the clearance concept as it is familiar in renal physiology.

Thus: alveolar ventilation per minute

$$= \frac{\text{CO}_2 \text{ output per minute}}{\text{fractional alveolar CO}_2 \text{ concentration}}$$

*or: $\dot{V}_A = \dfrac{\dot{V}_{CO_2}}{F_{A_{CO_2}}}$ where the units correspond.

Similarly, since oxygen is present in inspired air:

$$\dot{V}_A = \frac{\dot{V}_{O_2}}{F_{I_{O_2}} - F_{A_{O_2}}}$$

This assumes the respiratory exchange ratio to be unity which simplifies the equation.

*All symbols used are in accordance with the code agreed on in 1950 [*17*].

If tensions are used:

$$\dot{V}_A = \frac{\dot{V}_{CO_2}}{P_{A_{CO_2}}} \times k \text{ or } = \frac{\dot{V}_{O_2}}{P_{I_{O_2}} - P_{A_{O_2}}} \times k.$$

Rossier and Bühlmann, considering alveolar ventilation with respect to carbon dioxide alone, define it as being "the volume of air of alveolar composition embodying the total quantity of carbonic acid eliminated by respiration in the unit of time." A similar definition, changed to allow for the presence of oxygen in inspired air, would define alveolar ventilation with respect to oxygen. The weakness of this definition, however, lies in the impossibility of conceiving a value for "alveolar composition." For, when one rejects anatomic boundaries as a criterion of alveolar air, it is as abstract a concept as is physiologic dead space. It is failure to appreciate this which has led to much of the confusion about dead space.

The concept is clarified, although perhaps not simplified, if the clearance concept is applied to the pulmonary capillary blood. Thus, the definition in the case of CO_2 would be "the volume of air, whose components have the same tension as pulmonary capillary blood gases, which embodies the total quantity of carbon dioxide eliminated in unit time." As has been stated, the tidal volume cannot be divided into "physiologic dead space" and "physiologic alveolar volume" by the use of anatomic boundaries. Such a division can be effected if the concentration of one constituent gas is known in the mixed expired air and in each component part. Dead space gas has the composition of inspired air. "Alveolar" concentrations must be fixed independently; hence one is forced into defining "alveolar ventilation" in terms of blood concentration rather than in terms of a gaseous concentration in part of the lung. Once alveolar ventilation is defined in this manner, physiologic dead space follows immediately.

$$V_D = V_T - \frac{\text{alveolar ventilation}}{\text{respiratory rate}}$$

The implications of this concept have to be considered. The diffusion gradient across the alveolar membrane is neglected, the gradient showing itself, not as such, but as an increase in the dead space. Even the air in the best perfused alveoli is "relatively dead" by comparison with

the capillary. Secondly, if physiologic dead space is calculated in this way for several gases having the same site of diffusion, it will be higher for those that diffuse slowly.

The position is then that physiologic dead space cannot be defined for a gas unless the diffusion gradient for that gas appears, not as a gradient but as a dead space increment. Thus in the determination of steady state diffusing capacity for oxygen or carbon monoxide, where the alveolocapillary gradient is vital, one must obtain the alveolar concentration of the gas in question using a dead space independently derived. The dead space generally used is that obtained as just mentioned for carbon dioxide. This results in overestimation of diffusing capacity, as a small amount of diffusion gradient appears as dead space. Actually in normal subjects in whom 99 per cent equilibration between alveolus and capillary as regards carbon dioxide tension is achieved in 10 per cent of the transit time [*18*], and in whom venous admixture and ventilation/perfusion disparities are at a minimum, one would expect little difference between capillary carbon dioxide tension, arterial carbon dioxide tension and anatomic alveolar carbon dioxide tension. It was this which led Riley [*19*] to use arterial carbon dioxide tension in the derivation of dead space. Martin and Young [*20*] have shown by lobar spirometry that in a normal subject in the erect position there can be considerable variation in the ventilation-perfusion relations in the lung. They describe a case in which the physiologic dead space obtained in this way would exceed anatomic dead space by 100 ml. In view, however, of the closer agreement found by Holland and Blacket [*15*] between the normal mean physiologic dead space and the nitrogen meter dead space of Fowler [*21*], it is not believed that this is of frequent occurrence.

Another difficulty can now be resolved. Articles on diffusing capacity have discussed the assumption that dead space for carbon monoxide and oxygen is the same as for carbon dioxide [*15,18,22*]. However, according to the concept of physiologic dead space given here, this cannot be so. The important assumption is that the gases have the same site of exchange. Making this assumption and using carbon dioxide dead space for oxygen or carbon monoxide, the carbon dioxide exchange is used as the criterion of whether or not part of the lung can take part in oxygen or carbon monoxide exchange.

In all cases, then, the steady state diffusing capacity obtained using physiologic dead space must depart from the true diffusing capacity. The actual error introduced in this way in normal subjects is not great but it may account for some of the difference in values obtained by different methods.

The Meaning of Physiologic Dead Space in the Hamman-Rich Syndrome. The concept of dead space in this syndrome is likely to cause confusion if it is approached other than in the rigid manner already outlined. Its definition is still in terms of the capillary blood but the following points must be borne in mind:

The thickened alveolar walls: Forster [*18*] states that even if there is gross thickening of alveolar walls (up to ten times), 99 per cent equilibration of carbon dioxide between alveolus and capillary is achieved in 90 per cent of the transit time. Thus, end capillary blood would be in very good equilibrium with the adjacent alveolus, and the carbon dioxide tension of the mixed end capillary blood would be convenient to use in the calculation of a physiologic dead space. The small gradient present in this situation would make little difference to the dead space and there would be minimal effect on diffusing capacity. Mixed end capillary blood, of course, cannot be obtained, so in practice one has recourse to arterial blood. This is subject to the disadvantages detailed herein.

Venous admixture: This has not been measured in any proved cases of Hamman-Rich syndrome but the results of Austrian et al. [*10*] and Donald et al. [*11*] in various forms of fibrosis lead one to infer that it is present and is marked in the severe cases. Thus, the arterial carbon dioxide tension might well be up to 3 mm. Hg higher than the end capillary tension. This will lead to a higher value for physiologic dead space and a slightly high value for any diffusing capacity calculated using this.

The Application to Cases of Hamman-Rich Syndrome. The increase in dead space and in dead space/tidal volume ratio in the cases of the present series indicates that only about half of the ventilatory volume could be considered as coming into effective capillary contact for the purpose of oxygen or carbon monoxide transfer. As dead spaces were measured with respect to arterial blood, an arbitrary recalculation was made to obtain an approximation of dead space with respect to end capillary blood. For this, 3 mm. Hg was subtracted from the measured

arterial carbon dioxide tension. This is a generous allowance for venous admixture in view of the shape of the carbon dioxide dissociation curve and the low A-V CO_2 difference. Table II shows that while this results in a decrease in dead space, there is still gross elevation in the severe cases.

Recently Bates [*6*] has presented studies on three cases of the Hamman-Rich syndrome in which he has determined the $D_{L_{CO}}$ on exercise and hence the mean alveolocapillary gradient for oxygen. He found the gradient impossibly high and suggested that steady state methods for determining $D_{L_{CO}}$ may be invalid in this condition. He determined $P_{A_{CO}}$ by two methods; in the first, he used an assumed dead space and the Bohr equation; in the second, he used end tidal air sampling and obtained a value for $P_{A_{CO}}$ directly. However, Bates is unjustified in both the methods he used. The first, which involves the assumption of a dead space, is invalid owing to the high and unpredictable value for dead space in subjects at rest and on exercise. The second, which uses end tidal air as alveolar air is unjustified because of the high dead space/tidal volume ratio and because of the character of the dead space, areas of focal emphysema which contribute to the expirate right through expiration.

The use of the physiologic dead space as outlined will cause some slight overestimation of diffusing capacity, but the error introduced is less serious than that introduced by including a large contribution from regions which are not perfused in the alveolar sample. Regions which are not perfused have as little chance to contribute to oxygen or carbon monoxide transfer as have the nasal cavity and trachea, and hence must be excluded from consideration.

Clinical Effects of the Increased Dead Space. The increased dead space obliges the patient to ventilate much more in order to deliver sufficient air to the properly functioning regions of the lung. This effect at rest is no great embarrassment to the patient but it accounts, at least partially, for the resting hyperventilation which is so characteristic a feature of pulmonary fibrosis. On exercise the volume of dead space to be ventilated can become excessively great and it can play a major part in bringing the patient to the dyspnea level at relatively low levels of exercise. The correlation of the dead space with the clinical severity of the cases was previously noted and, while many other factors play a part in the production of symptoms, it is believed that the importance of the high dead space has not been sufficiently stressed.

SUMMARY

Physiologic dead space has been measured in five cases of the Hamman-Rich syndrome using arterial carbon dioxide tension for alveolar carbon dioxide tension.

At rest physiologic dead space was increased in three cases, sometimes grossly. The dead space/tidal volume ratio was elevated in all cases. On exercise physiologic dead space increased greatly; its ratio to tidal volume showed no appreciable change from the resting ratio and was excessive in all cases.

The increase was too great to be accounted for by errors in the method or an artefact caused by venous admixture. It is attributed to the development of focal emphysema.

Increase in dead space correlates well with, and is believed to account partially for, clinical severity.

In this condition the dead space is too high at rest and on exercise for one to obtain "alveolar air" by end tidal sampling. Similarly the assumption of a dead space is unjustified.

The meaning of "physiologic dead space" is discussed. Attention is drawn to the fact that it must be defined in terms of blood gas and not alveolar gas tensions, since the term itself implies our inability to choose any sample of air as representative of alveolar air.

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Mechanisms of Anemia in Leukemia and Malignant Lymphoma*

JANE F. DESFORGES, M.D., JEAN D. ROSS, M.D. *and* WILLIAM C. MOLONEY, M.D.
Boston, Massachusetts

ANEMIA may be the first and is often the most prominent manifestation of malignant lymphoma and leukemia, and frequently its severity is out of proportion to the extent of involvement by the primary disease. It is the purpose of this paper to describe the mechanisms of development of this complication and to discuss the management of anemia in these disorders.

METHODS AND MATERIALS

Technics used for routine blood studies, for immunohematologic observations, for Ashby and Cr^{51} tagged red cell survival times and for the investigation of plasma and red cell iron turnover have been previously described [*1*]. The normal limits for the ferrokinetic indices are included in the table. During the first part of the project, surface scanning of heart, liver, spleen, sacrum and thigh was performed with a Geiger-Mueller probe and the results at each site were expressed as percentage of the total counts from the five areas [*1*]. In later studies we employed a Tracerlab scintillation monitor, with a 1-inch window and a 2-inch lead shield projecting 2 inches beyond the window. This was held in a constant position against the standard areas marked on the skin each time observations were made. These results were then expressed as absolute counts per minute after correcting for background and physical decay.

The patients described in the text were seen in the Hematology Laboratory (Tufts) of the Boston City Hospital, and the diagnoses were established by blood and bone marrow morphology, histochemistry and tissue biopsy.

RESULTS

The most common erythroid defect encountered in our cases of malignant lymphoma and leukemia was hemolysis, which was present in varying degree. This was demonstrated by measuring the rate of destruction of either the patient's erythrocytes tagged with Cr^{51} and autotransfused or those of normal donors studied by the same methods, or by the differential agglutination technic. Hemolysis of erythrocytes from both normal donors and the patient was observed, thus demonstrating that an extracorpuscular defect is involved in the hemolytic mechanism.

Clinically, leukemia may first manifest itself as acquired hemolytic anemia, and this was documented by one patient in this study who had mild anemia, reticulocytosis and a positive Coombs' test, together with splenomegaly, many months before leukemia could be recognized in either marrow or liver biopsy. During this period the red cell survival time measured by the Ashby technic (normal equals 120 days) indicated a red cell life span of less than two weeks. In spite of this the erythropoietic response was such that the patient's hematocrit was between 38 and 40 per cent during most of this phase of the disorder.

Survival of Cr^{51}-transfused cells in this series of patients with malignant lymphoma and chronic lymphatic leukemia has been plotted in Figure 1. While splenomegaly was prominent in three of these cases, it is noteworthy that the patient, whose red cells had a half-time of seventeen days, had Hodgkin's granuloma confined to the thorax without splenic involvement. In none of these cases was there serological evidence of immunohemolysis by Coombs' test or by the presence of autoagglutination or cold agglutination. The compensatory capacity of the marrow in these cases was demonstrated by the adequate hematocrits. It is evident that a significantly increased rate of erythrocyte destruction may be associated with only mild anemia in the presence of adequately functioning marrow.

That there may be a variable response to

* From the Tufts Hematology Laboratory and the First and Third (Tufts) Medical Services, Boston City Hospital, Boston, Massachusetts. This investigation was supported by Research Grant #C-3171 from the National Cancer Institute, Public Health Service.

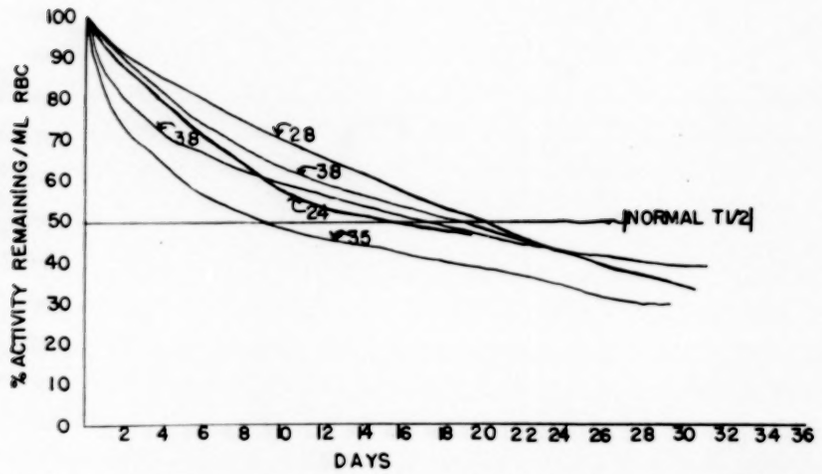


FIG. 1. The survival time of Cr^{51} tagged red cells is plotted in a group of patients with lymphatic leukemia and lymphoma. The radioactivity remaining in the circulating red cells is expressed as percentage of that observed five hours after injection. The normal values for disappearance of half the activity is noted as normal $T\frac{1}{2}$. The hematocrit at the time of the study is noted on each curve.

TABLE I

DATA ON IRON TURNOVER IN PATIENTS WITH LEUKEMIA AND LYMPHOMA

Case (no.)	Disease	$T\frac{1}{2}$* (min.)	Serum Iron (μg. %)	Packed Cell Volume (%)	Plasma Iron Turnover			Red Cell Iron Turnover		
					Total (mg.)	Red Blood Cells/ml. (μg.)	Whole Blood Cells/ml. (μg.)	Total (mg.)	Red Blood Cells/ml. (μg.)	Whole Blood Cells/ml. (μg.)
I	Chronic lymphocytic leukemia	16	51	29	143	88.5	23.4	143	88.5	23.4
II	Chronic lymphocytic leukemia	295	231	25	33	25.0	5.9	0	0	0
III	Myeloma	190	200	21	33	39.2	8.2	11.2	13.3	2.8
IV	Acute leukemia	250	142	26	14.4	17.7	4.2	3.2	3.9	0.9
V	Acute leukemia	225	216	29	32.2	26.8	9.0	13.5	11.3	3.78
VI	Acute leukemia	130	170	22	50	51.8	10.3	11.0	11.4	2.3
	Myeloproliferative disorders:									
VII	Chronic myelogenous leukemia	192	167	20.5	3.1	3.7	0.8	0	0	0
VIII	Myeloid metaplasia	30	68	21	85	95.5	18.1	68.8	77.0	14.6
IX	Myeloid metaplasia	60	137	29	82	62.8	16.7	77.9	59.6	15.9
X	Chronic myelogenous leukemia	34	111	38	137	61.7	21.1	37.5	23.1	7.9
XI	Polycythemia vera and myeloid metaplasia	12	60	51	121	46.5	24.0	121	46.5	24.0
XII	Polycythemia vera	108	135	40	28.3	17.8	6.8	28.3	17.8	6.8
	Normal range:									
	High	200	...	....	42.7	24.35	10.95	.....	17.60	7.93
	Low	72	...	....	27.5	16.6	7.77	.....	12.48	5.75

* $T\frac{1}{2}$ refers to the time in minutes of the disappearance of half the injected Fe^{59} from plasma. Both plasma and red cell iron turnover are given in relation to red cell volume and whole blood volume, with the range of values in normal, non-anemic persons for comparison. The values are calculated for a twenty-four hour period and are expressed in milligrams for the total, and in micrograms per milliliter of red cells or whole blood.

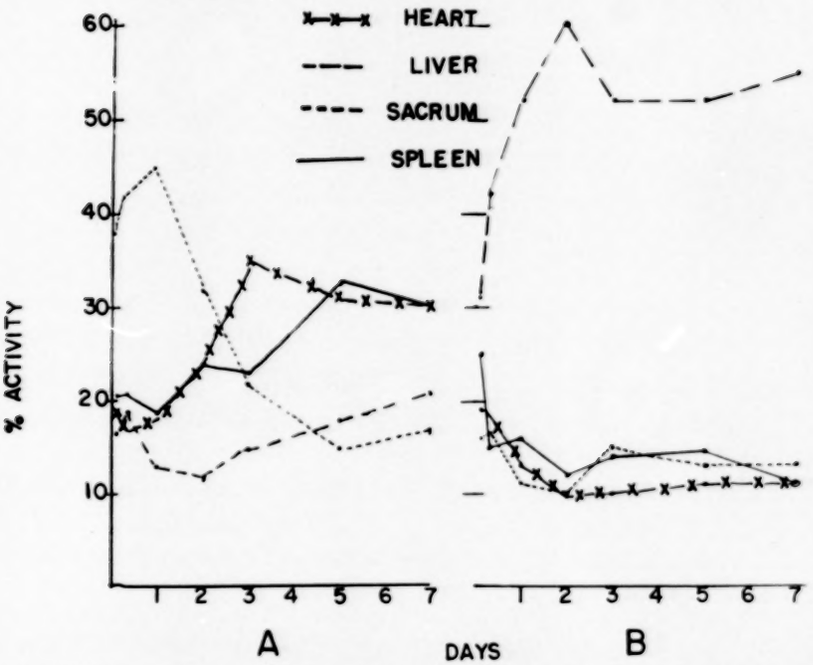


FIG. 2. The radioactivity observed over the indicated sites after injection of plasma-bound radioactive iron is plotted according to time and days after injection. Radioactivity is expressed as per cent of the total counts at the indicated sites at the time of observation. A is Case I and B is Case II. In A there is normal marrow uptake and discharge of radioactive iron with reappearance in circulating blood. In B there is insignificant marrow uptake with consequent storage in the liver.

hemolysis is also demonstrated by measurement of the iron turnover in these diseases. In Table I, contrasting erythropoietic responses in two cases of chronic lymphatic leukemia are presented. Case I had an hematocrit of 35 per cent and a reticulocyte count of 3.5 per cent red cells with a white count of 22,000 per cu. mm. at the time of this study. In this patient the half-time of plasma iron disappearance was sixteen minutes with a total plasma turnover of 143 mg. a day. One hundred per cent of the injected radioiron reappeared in the circulating red cells, with resulting values for red cell iron turnover of 88.5 μg. per ml. of red cells and 23.4 μg. per ml. of whole blood. Such values are markedly increased, indicating very active erythropoiesis. The fact that there was anemia at the time of this study demonstrates that the compensatory increase in erythropoiesis was inadequate. In Figure 2A are plotted the dynamics of the radioactive tag in this case, as estimated by surface monitoring of liver, sacrum, spleen, precordium and thigh. The curves demonstrate a rapid uptake of iron by the marrow, followed by a rapid decline in activity as the radioactivity appeared in the circulating red cells. In contrast to this, as shown in Figure 2B, are the results of surface scanning for Fe^{59} in Case II, a patient with chronic lymphatic leukemia in relapse maintained by transfusion therapy. At the time of these observations this patient's hematocrit was 29 per cent, reticulocytes were less than 0.1 per cent, and the white count was 98,600 per cu. mm. The lack of incorporation of Fe^{59} into the red cells and the accumulation of the tagged iron in the liver area are consistent with marked depression of erythropoiesis and consequent iron storage in the liver. Both these findings and the tabulated calculation for iron turnover indicate that erythropoietic activity was diminished.

Marrow hypofunction was observed also in multiple myeloma (Case III) and this appeared to be the basis for the anemia. In this instance marrow specimens contained both myeloma cells and normal marrow elements but the extent of total marrow replacement could not be precisely estimated.

In certain cases of acute leukemia, ferrokinetic indices indicated a severe depression of eryth-

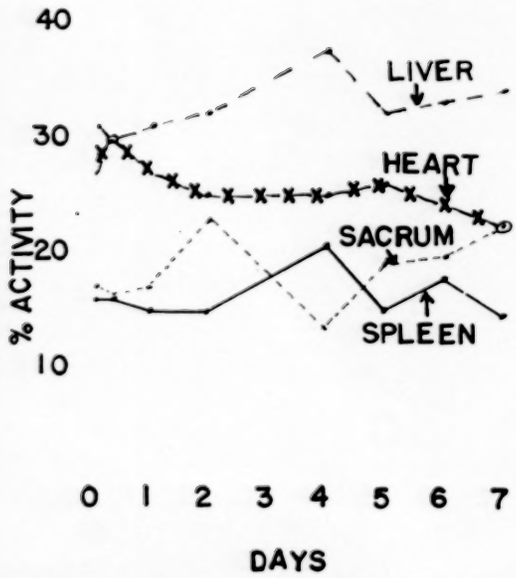


FIG. 3. This chart is plotted in the same manner as Figure 2. It demonstrates depressed marrow uptake with deposition of iron in the liver in Case VI.

ropoiesis, probably explained in these instances by replacement of normal marrow elements by leukemic tissue. The values observed in Case IV are tabulated to illustrate marked depression of red cell iron turnover in association with extensive leukemic infiltration of the marrow.

However, this depression of erythropoiesis cannot always be explained on an anatomic basis. In Case V, for example, the marrow was hypocellular throughout the course of the disease, and the only evidence of leukemia for many months was the presence of small clumps of monoblasts scattered through the hypocellular marrow specimens. In Case VI, a patient presenting with severe anemia, many normal elements were still apparent in the marrow early in the disease, although there was marked insufficiency of marrow function at this time as evidenced by diminished red cell iron turnover, consistent with decreased erythropoiesis. Figure 3 is an example of the postinjection fate of Fe^{59} as observed by surface monitoring in one of these patients. The curves are similar to those in Figure 2B, illustrating a case in which there was increased iron deposition in the liver and depressed marrow uptake.

Corticosteroid therapy was ineffective in stimulating erythropoiesis in those cases presenting as aplastic anemia. When anemia was due to marrow replacement by infiltrative disease, response to therapy depended upon the degree of control of the underlying process.

Patients with myeloproliferative disorders have shown a variety of erythropoietic defects. The variability of red cell survival in these syndromes is demonstrated in Figure 4. At one extreme is a case with normal red cell survival time in the presence of moderate anemia, at the other are patients with a rather striking hemolytic process. In all instances splenomegaly was marked.

Examples of ferrokinetic data in a group of patients with these disorders are presented in the table. Case VII is an example of a patient with chronic myelogenous leukemia in whom the

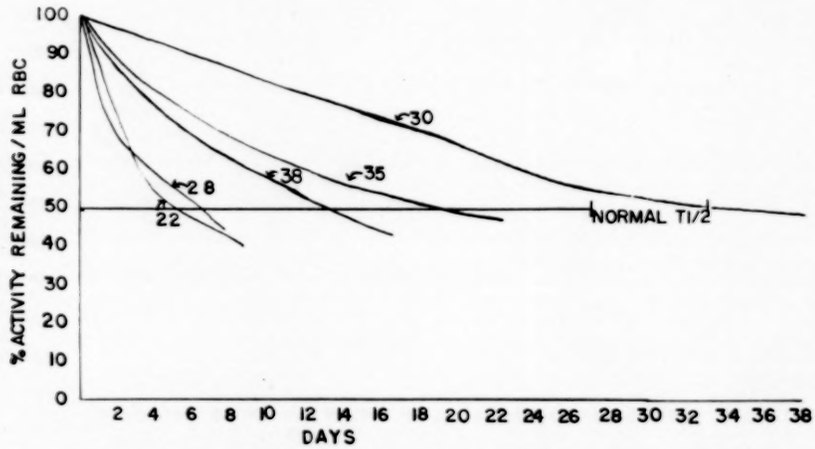


FIG. 4. The survival time of Cr^{51}-tagged red cells is plotted in a group of patients with myeloproliferative diseases. The radioactivity remaining in the circulating red cells is expressed as percentage of that observed five hours after injection. The normal values for disappearance of half the activity are noted as normal $T\frac{1}{2}$. The hematocrit at the time of the study is noted on each curve.

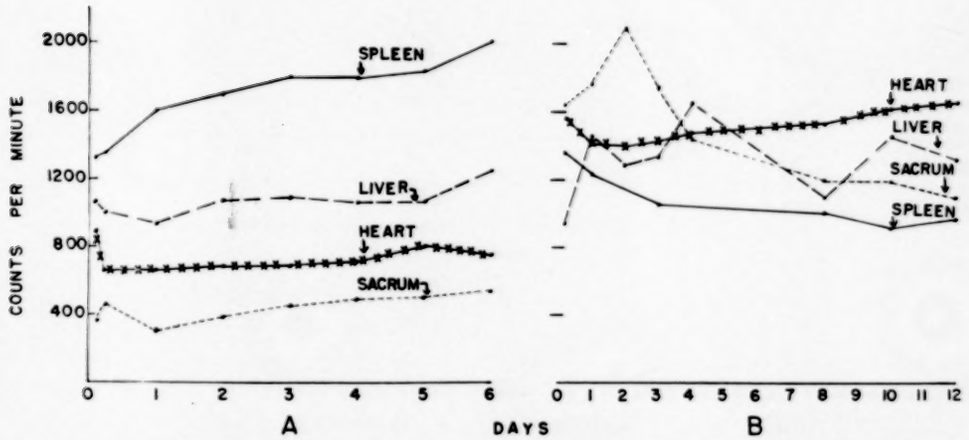


FIG. 5. The radioactivity observed over the indicated sites after injection of plasma-bound radioactive iron is plotted according to time and days. Radioactivity is expressed as counts per minute corrected for physical decay. A is Case VIII. In this figure there is immediate concentration of radioactivity over the spleen without subsequent discharge. B, Case XII, demonstrates normal uptake and release by marrow with increasing activity over the heart.

etiology of the anemia was complicated by bone marrow depression possibly related to prolonged therapy with Myleran.®* The depression of erythropoiesis, as evidenced by plasma and red cell iron turnover, was profound. This was further documented by surface monitoring which revealed deposition of the iron in the liver and lack of bone marrow uptake without evidence of ectopic erythropoiesis in the spleen. In contrast to this, a patient with "agnogenic" myeloid metaplasia. (Case VIII), was found to have a very active red cell iron turnover; however, in spite of the elevation of these values above normal in this case, anemia was present. This is explained by the fact that the patient had a severe hemolytic process, documented by a simultaneous Cr^{51}-erythrocyte survival half-time of seven days. The patient had very marked splenomegaly, and surface monitoring revealed splenic uptake suggesting active erythropoiesis in this organ. (Fig. 5A.) In this figure it is noteworthy that the radioactivity which was concentrated in the splenic area as it disappeared from the plasma remained there throughout the course of experiment; this suggests two possibilities: first, that intrasplenic erythropoiesis may have been occurring, with immediate sequestration and destruction of the newly formed cells, or second, that the red cells may have been released into the circulation only to reaccumulate in the spleen and to be destroyed there. Possibly both processes were at work. Splenic radiation in this patient was associated with a decline in hematocrit and in reticulocyte count as well as in leukocytes, suggesting depression of erythropoiesis by this therapy. In another patient with myeloid metaplasia (Case IX) there also was ferrokinetic evidence of increased red cell iron turnover, and surface monitoring revealed activity consistent with intrasplenic erythropoiesis. Simultaneous red cell survival studies again demonstrated hemolysis, the red cell Cr^{51} half-time being seven days. In Case X, an instance of chronic myelogenous leukemia, the ferrokinetic data are similar, except for the decreased percentage of labeled plasma iron reappearing in the circulation. Monitoring revealed this iron to be in both liver and spleen for the duration of the study, probably at least in part reflecting extramedullary hematopoiesis with superimposed hemolysis.

Polycythemia vera may show various patterns. In Case X, a patient with polycythemia vera and a normal white count associated with immature myeloid and erythroid cells in the peripheral blood and marked splenomegaly, the iron turnover was strikingly increased. In this patient the erythropoietic activity compensated for premature red cell destruction, and high normal red cell values were maintained. External monitoring during these studies revealed two sites of erythropoiesis, the spleen and the bone marrow, but technical limitation of these observations made it impossible to say which was the more effective erythropoietic organ. The effects of therapy in polycythemia vera are demonstrated in Case XI, a patient with polycythemia vera

* 1:4 Dimethone sulphonyl oxybutane.

controlled by P^{32}. The iron turnover values noted are within normal limits, and surface monitoring revealed normal uptake and discharge of the Fe^{59} (Figure 5B).

Thus, as a rule in these syndromes the ability of the marrow to produce compensatory erythropoietic response determines the degree of anemia. In myeloproliferative disease, extramedullary erythropoiesis may play a significant part in this response.

COMMENTS

Cases are described in this report in which hemolytic anemia or refractory anemia was the most pronounced abnormality apparent before clear evidence of leukemia was available. It is well known that leukemic disease may first manifest itself as anemia or pancytopenia, and preleukemic states have been reported in which the clinical picture is either that of aplastic anemia or the opposite extreme, that of acquired hemolytic anemia associated with increased erythropoietic activity [*2–6*]. Such preleukemic cases often present many problems in diagnosis.

More commonly, anemia occurs when the underlying disease is already obvious. In overt malignant lymphoma and leukemia, both hemolysis and marrow insufficiency may play a role in the pathogenesis of anemia. Red cell survival studies in a series of patients with these diseases have demonstrated that there is usually mild hemolysis [*7–9*] and with the use of Fe^{59} a relative marrow erythropoietic insufficiency has been demonstrated in similar cases [*8,10,11*]. Anemia in other forms of malignancy has also been investigated and here, too, it is suggested that the anemia is out of proportion to the anatomic involvement and stems from mild hemolysis together with relative marrow insufficiency [*12–14*].

Serological evidence of immunohemolysis has been obtained in a number of cases of lymphatic leukemia and lymphoma; the general subject has been reviewed by Rosenthal [*15*]. The postulated close relationship between lymphatic disease and gamma globulin production allows speculation concerning a possible source of these abnormal proteins. Experiments of Pirofsky [*16*] suggest that the malignant lymphocyte could be a source of a hemolysin or an agglutinin and thereby lead to premature destruction of the red cells. Crosby et al. [*17*] have demonstrated *in vitro* an abnormal hemolytic system associated with malignant disease. Whether such factors have *in vivo* significance is not established.

Occult hemolytic anemia without evidence of serological abnormality is a much more common complication [*7–9,12,14,16,19*], and in such instances the degree of hemolysis can be documented only by observations of red cell survival or inferred from calculation of red cell renewal rates using Fe^{59}. The findings in our series of patients confirm the reports that hemolysis of mild or moderate degree is frequent in both lymphatic and myeloid disease. The relation of the hemolytic tendency to splenomegaly has been stressed [*7*] but the association is not invariable. In this series hemolysis was observed in the absence of a palpable spleen.

The observations of red cell survival and iron turnover in this group of patients makes it clear that the capacity of the marrow to respond determines the degree of anemia. At one extreme are the cases of acute leukemia with marrow infiltration and probably almost complete replacement by leukemic tissue, resulting in relatively complete cessation of erythropoiesis and an anemia which could be designated as primarily aplastic. Only when treatment affects the underlying disease by inhibition of the leukemic or lymphomatous process does erythropoietic function return. Of more complex etiology is the anemia due to marrow hypofunction unexplained by anatomic replacement. One might postulate both the aplasia and leukemia to be the result of action of toxins, chemical, physical or other, to which the myeloid tissue has been exposed in the past. However, accurate documentation of such exposure is usually impossible. Such patients are extremely resistant to all forms of therapy.

At the other extreme, as pointed out in this study, are cases in which hemolysis was present and yet increased erythropoiesis enabled the patients to maintain normal or almost normal hemoglobin levels. This was seen in the early stages of both myeloid and lymphatic disease.

In myeloproliferative syndromes the disease process alone may explain hypofunction of the marrow on the basis of myelofibrosis, a common accompaniment of myeloid metaplasia. It should be noted that in one patient the anemia progressed rapidly after splenic radiation. This effect seemed to be explained by depression of splenic erythropoiesis in a patient with inadequate myeloid tissue, although a possible systemic effect of local splenic radiation cannot

be excluded. There is, however, abundant evidence to support the view that ectopic splenic erythropoiesis in this syndrome is not simply compensatory, and the ability of a seemingly hypofunctioning marrow to produce red cells after splenectomy is unpredictable [*20–22*].

In the case of myeloid leukemia, the striking hypofunction of the marrow associated with pathological evidence of marrow hypoplasia followed therapy with Myleran, and may have been due to the toxic effect of this drug on the marrow. A similar case has recently been described by Unugar, Schulman and Dameshek [*23*]. However, patients with chronic myelogenous leukemia untreated with chemotherapeutic agents have been found at autopsy to have myelofibrosis and myelosclerosis.

Thus, the anemia noted in malignant lymphoma, leukemia and myeloproliferative disorders is due to the combined circumstances of hemolysis and inability of the marrow to compensate fully for this. While marrow insufficiency is often explained simply by anatomic replacement, it may occur in the absence of any infiltrative process and thus apparently be related to the more subtle biochemical alteration of factors which govern erythropoiesis.

The success of therapy for the anemia in these disorders usually depends on the effectiveness of control of the underlying disease. However, occasionally hemolysis is very marked, demanding treatment directed primarily at this. Corticoids may give temporary control in such instances; rarely, splenectomy has been attempted and found effective [*24–27*]. When the clinical picture is that of hypoplastic anemia, therapeutic attempts to stimulate erythropoiesis have been ineffective and transfusion therapy has been the only means of treatment.

SUMMARY

This investigation into the mechanism of anemia in leukemia, malignant lymphoma and myeloproliferative disorders has shown that a hemolytic process is frequently present. The erythropoietic response of the bone marrow to anemia in these circumstances is variable. Diminished erythropoiesis is usually explained by replacement of the marrow by malignant cell proliferation but in some cases the mechanism of marrow hypofunction can not be adequately established.

Unless the underlying disease process can be controlled by chemotherapy or other measures, the treatment of anemia in these malignant and myeloproliferative disorders is usually unsatisfactory, and recourse must be had chiefly to transfusion therapy.

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Review

The Pathologic Physiology of Chronic Bright's Disease*

An Exposition of the "Intact Nephron Hypothesis"

NEAL S. BRICKER, M.D., PETER A. F. MORRIN, M.B., B.CH. *and* S. WESLEY KIME, JR., M.D.
St. Louis, Missouri

THE course of advancing chronic renal disease is characterized by the development of a constellation of clinical, biochemical and physiologic derangements. These derangements may ultimately involve many organs and organ systems; however, the fundamental event underlying their development is the progressive destruction of nephrons. Although the causal relationship between intrinsic renal disease and the complex abnormalities of the uremic state was recognized by Bright more than twelve decades ago [*1*], the precise nature of the events leading from the initial destruction of nephrons to the picture of terminal uremia is yet to be fully understood. Until it becomes possible to prevent the various forms of chronic renal disease or to interrupt their inexorable progression, a major requisite to effective concepts of therapy is the clarification of the sequential events in pathologic physiology. In this regard it is essential to define clearly the functional capacity, range of operation and limitations of the diseased kidney. The present discussion consists of a review of recent experimental observations relating to these considerations.

THE TERM, "CHRONIC BRIGHT'S DISEASE"

The observations of Bright, establishing the relationship between chronic renal disease and the clinical abnormalities of the uremic state [*1*], may well be regarded as the beginning of the modern era of the study of diseases of the kidney. It seems appropriate, therefore, that the term, chronic Bright's disease, is generally employed (and will so be used in the present discussion) as a generic expression for all the chronic pathologic disorders of the kidney that lead to progressive renal failure. In this context the term assumes conceptual as well as historic significance, for it tends to group together a number of diseases of diverse etiology, differing pathogenesis and widely varying pathologic characteristics. A singular term implies the existence of a common denominator in these disease entities which supersedes their differences. There is now abundant evidence, both clinical and experimental, to support the view that the many different forms of chronic renal disease may give rise to the same pattern of chemical and functional derangements, the evolution of which relates principally to the rapidity and extent of nephron destruction. Although in certain instances specific alterations in function may correlate with involvement of a particular site of the nephron,† the major parameters of function are similar in all forms of chronic Bright's

† Several examples of these exceptions may be cited: (1) During the natural history of chronic glomerulonephritis, lupus nephritis and certain other chronic renal diseases, a marked increase in glomerular permeability to protein may result in the evolution of a nephrotic syndrome. (2) Acute glomerulitis (e.g., secondary to an acute exacerbation of chronic glomerulonephritis, malignant hypertension, etc.) may modify glomerular tubular balance in the residual functioning nephrons of the diseased kidney and evoke corresponding functional changes. (3) A number of disease entities exist in which disproportionate involvement of one or more specific tubular functions may dominate the clinical picture [*2*].

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disease, and in general the more advanced the pathologic process becomes, the less evident are the differentiating features. From the functional point of view, therefore, consideration of the various forms of chronic renal disease as members of a unified group serves to emphasize the fact that the evolution of abnormalities is in most instances independent of etiology or details of morphologic change; moreover, it suggests that the *functional capacity of the residual nephrons of the diseased kidney* is largely independent of the specific form of renal disease. Accordingly, in the present discussion, concepts of pathologic physiology will be considered without systematic reference to the etiology of the underlying renal disease.*

THE FUNCTIONAL CAPACITY OF THE DISEASED KIDNEY

General Considerations. In the normal subject the renal contribution to homeostasis is shared by approximately 2 million nephrons. In chronic Bright's disease the total nephron population diminishes progressively. Interpretation of the contribution to homeostasis must therefore involve two considerations: one, *the consequences of nephron destruction* and two, *the functional capacity of the persisting nephrons*. The decrease in the number of nephrons is clearly responsible for many of the abnormalities that develop in the patient; the persisting nephrons permit the patient to survive.

THE CONSEQUENCES OF NEPHRON DESTRUCTION

Because the over-all functional capacity of a kidney relates to the total number of intact functioning nephrons, the ablation of nephrons has definite and predictable consequences.

The Increasing Demands on the Residual Nephrons. As the number of constituent nephrons decreases, each residual nephron must perform a greater fraction of total renal function. If balance of any specific solute is to be maintained (and retention in body fluids avoided) on a constant intake, the quantity excreted by each nephron must increase as the total population of functioning nephrons decreases. The facility with which this is accomplished varies with the nature of the particular mechanism responsible for renal excretion.

Substances excreted by active transport mechanisms: Balance and plasma concentrations of solutes which are either secreted or reabsorbed by active tubular transport mechanisms may be maintained within normal limits only if the *rate of transport per nephron* is altered as the number of nephrons contributing to function diminishes. For substances which are excreted principally by tubular secretion, constancy of body fluid levels demands an increased secretory rate per nephron. For substances which are actively reabsorbed, reabsorption per nephron must decrease if balance is to be maintained on a given intake. For the majority of transport systems thus far studied, appropriate adaptive changes in excretion occur, and abnormalities in body fluid concentrations of the specific solutes are minimized or, in some instances, prevented until the late stages of chronic Bright's disease. Examples of two such adaptations may be cited.

Potassium is excreted principally by tubular secretion [*3*]. On any given dietary intake of potassium each nephron in the normal kidney must excrete approximately 1 two-millionth of the total quantity. In the patient with only 200,000 functioning nephrons, all other factors remaining constant, the same potassium intake demands that each nephron increase its excretion rate by tenfold. The diseased kidney must therefore function at a level that the normal kidney is called upon to achieve only rarely. This is ordinarily achieved, and hyperkalemia is an infrequent occurrence until the terminal stages of chronic Bright's disease [*4*].

Phosphate represents a substance which is reabsorbed by an active tubular transport mechanism [*5,6*]. In the normal subject approximately 85 to 90 per cent of the filtered phosphate is reabsorbed and the amount excreted is balanced with intake and metabolic needs so as to maintain constancy of plasma phosphorus concentrations. As the nephron population (and hence total glomerular filtration rate [GFR]) diminishes, the filtered load of phosphate falls in parallel. Were the transport mechanisms to continue to reabsorb 85 to 90 per cent of the filtered phosphate, excretion would decrease progressively and retention of phosphate would occur early in the course of chronic Bright's disease. (At a filtration rate of 50 ml./minute and a plasma phosphate level of 4 mg.

* Such a unified approach in no way minimizes the importance of recognizing the differentiating features in etiology, pathogenesis and pathologic characteristics. However, a discussion of these considerations is beyond the scope of the present paper.

per cent, reabsorption of 85 per cent of the filtered load would permit excretion of approximately 450 mg./day rather than the 700 to 800 mg. required to maintain balance on a normal diet.) However, phosphate reabsorption in the residual nephrons does not remain constant but decreases in a manner so precise as to allow a diminished number of nephrons to continue to maintain phosphorus balance. Plasma phosphate concentrations may remain normal until the filtration rate falls as low as 25 ml./minute [7]. At this level of renal function approximately 50 per cent of the filtered phosphate must be excreted in order to preserve normal plasma levels. At lower levels of GFR suppression of reabsorption is not sufficiently great to prevent phosphate retention on a normal phosphorus intake.* Thus hyperphosphatemia ultimately appears, but only after the nephron population is markedly reduced.

Substances excreted by glomerular filtration: For substances which are excreted predominantly by glomerular filtration, without the intervention of active transport mechanisms, a decrease in the number of nephrons must result in retention in body fluids if the rate of acquisition remains constant. This is illustrated by the progressive rise in plasma concentrations of two end products of metabolism, urea and creatinine. Both substances enter body fluids at a relatively constant rate in normal and uremic subjects if the dietary intake and cellular catabolism remain constant. The major determinant of the amount excreted is the glomerular filtration rate. Thus the total amount entering the functioning nephrons (i.e., the filtered load) represents the product of the plasma concentration times the glomerular filtration rate. In a person with normal kidneys, plasma levels remain essentially stable over prolonged periods by virtue of the fact that the amount excreted each day equals the amount acquired. In the patient with chronic Bright's disease, each period of nephron destruction is accompanied by a corresponding decrease in total glomerular filtration rate.† The filtered load of urea or creatinine is thereby decreased, and this in turn results in a decrease in the total amount excreted. With a constant rate of production and a decreased rate of excretion, retention is an inevitable consequence.

As the plasma levels rise the filtered load entering each residual nephron increases until ultimately the rate of excretion again equals the rate of production. At this point a new steady state is established and plasma levels will stabilize (although at a higher than normal level) until additional destruction of nephrons causes a further decrease in the total filtration rate. If nephrons are destroyed continuously, urea and creatinine concentrations rise progressively. If nephron destruction is intermittent, the rise occurs in a step-wise pattern.

The effects of nephron destruction on the patterns of excretion of other substances (principally sodium chloride and water) will be considered in detail subsequently.

The Decreased Range of Excretion. A second major consequence of the destruction of nephrons is a decrease in the range of excretion for any given substance. Although each individual nephron in the diseased kidney may be capable of increasing or decreasing the excretion rates of specific solutes or of water in response to the needs of the patient, the absolute change in excretion rates is determined by the product of the *change per nephron* times the *total number of functioning nephrons*. Hence, the fewer the remaining nephrons, the smaller will be the range over which excretion rates of any substance may vary. The upper limit of excretion for all substances will be decreased. Moreover, because of the adaptive changes that enable a decreased number of nephrons to excrete relatively normal amounts of sodium, chloride and water for long periods (these will be considered subsequently), the ability to decrease excretion rates is also restricted. Thus the lower limit of excretion is above that of the normal subject, and an obligatory renal excretion of salt and water may continue despite an inadequate intake and/or loss of body fluids through sweating, vomiting or diarrhea.*

It is apparent that the functional capacity of the residual nephrons of the diseased kidney determines the degree to which homeostasis is preserved. It thus becomes essential to examine in detail the quantitative aspects of renal function of the diseased kidney.

* At a filtration rate of 10 ml./minute and a plasma phosphate concentration of 4 mg. per cent, the excretion into the urine of 100 per cent of the filtered phosphate would equal only 575 mg./twenty-four hours.

† The possibility that GFR per residual nephron may increase as an adaptive change in the diseased kidney will be discussed in a subsequent section.

* The concept of an upper and lower limit of excretion rates has been admirably developed and discussed by Talbot and associates [8,9].

THE FUNCTIONAL CAPACITY OF THE SURVIVING NEPHRONS OF THE DISEASED KIDNEY

A Statement of Conflicting Views. The degree to which function is preserved in the persisting nephrons of the chronically diseased kidney has become the subject of much controversy. Perhaps the most widely held view is that morphologic disorganization of the renal parenchyma results in extensive abnormalities in intrinsic renal functions. Specific functional limitations in the diseased kidney (e.g., inability to concentrate and dilute urine, inability to excrete a sodium-free urine, and the like) are generally attributed to anatomic involvement of active sites in the persisting nephrons. Within recent years an increasing amount of evidence has accrued which seriously challenges this concept. The observations from many sources suggest that *the surviving nephrons of the diseased kidney largely retain their essential functional integrity*. Accordingly, a thesis diametrically opposite to the conventional view has arisen. According to this thesis the nephrons in the diseased kidney are reduced in number but possess essentially normal functional characteristics. The limitations of the diseased kidney would therefore relate not to intrinsic functional defects but rather to a predictable series of events that evolve when a decreasing population of relatively normal nephrons must maintain homeostasis.

Resolution of this conflict has important practical implications. If the functional systems of the diseased kidney deteriorate in a chaotic manner any attempts to develop a unified concept of pathologic physiology and to derive therefrom a rational therapeutic program would be complicated, perhaps hopelessly so. However, if the surviving nephrons in the diseased kidney are basically intact, a clear definition of the capacity and range of operation of these units at any given stage of chronic renal disease may permit a formulation of sound principles of therapy.

THE "INTACT NEPHRON" HYPOTHESIS

A number of investigators in the past have alluded to the possibility that the persisting nephrons in the diseased kidney are functionally intact. In 1939 Hayman and co-workers [*10*] demonstrated that removal of one intact kidney and one-third of the other kidney in the dog is associated with the development of polyuria and relative inability to concentrate the urine. They emphasized that isosthenuria may develop in the absence of abnormalities in the renal epithelial cells and suggested that the latter need not be invoked to explain the isosthenuria of chronic renal disease. Platt [*11*] has defended vigorously the concept that the residual functioning nephrons may be capable of normal activities. Moreover, he has suggested that as the renal mass (and therefore the number of remaining nephrons) diminishes, the persisting units may undergo functional adaptations that enhance their ability to defend the integrity of body fluids. More recently many other investigators, including Merrill [*12,13*], Welt [*14*], Rosenheim [*15*] and Strauss [*16*] have supported the thesis that the remaining nephrons of the chronically diseased kidney may retain many normal functional characteristics.

The diseased kidney behaves in an orderly and predictable manner. During periods of relative stability (i.e., when nephrons are not being destroyed rapidly) the patient with advanced renal failure is able to excrete the same amount of urea, creatinine, phosphate, sodium, chloride, potassium and other solutes as does the subject with normal kidneys. For substances which are excreted predominantly by filtration and do not depend upon active tubular transport processes, increased plasma levels alone will account in large part for the normal excretion rates. However, for substances which are handled by active tubular transport mechanisms, normal excretion by a decreased number of nephrons demands a high degree of functional efficiency.

Until recently precise definition of the functional capacity of the nephrons of the diseased kidney has been hampered by a number of technical obstacles. Among these, three have been of major importance. First, it has rarely been possible to relate data from the patient with chronic Bright's disease to control observations from the same subject. Because of this it has been necessary to compare values for renal function in patients with control values derived from normal subjects. Second, it has been difficult to establish the true relationship between clearance values and specific renal functions in the severely diseased kidney. The possibility that nephrons with intact glomeruli may have damaged tubules which permit inulin or creatinine to back-diffuse, or that nephrons with contracted glomeruli have intact tubules which secrete PAH normally, has not been definitely excluded because of the lack of appropriate control meas-

urements. Third, certain of the chemical changes in the uremic patient, in particular the high plasma urea levels, may influence renal function in such a way as to interfere with assessment of the inherent ability of tubular transport systems.

Recently an experimental model has been employed which appears to obviate these technical difficulties [*17–25*]. Experiments have been performed on dogs with experimentally induced chronic renal disease. In each animal the renal lesion was induced in a single kidney and the contralateral organ was maintained intact. By virtue of a surgical procedure which allows the formation of two separate and permanent urinary bladders, the individual kidneys may be studied simultaneously and serially. Observations obtained before the induction of the unilateral lesion provide the required baseline data. In all studies performed after induction of the lesion the functions of the diseased kidney may be compared with those of a normal organ subjected to identical environmental conditions and extrarenal stimuli. This comparison has two advantages: (1) It permits a quantitative assessment of the integrity of a variety of renal functions in the diseased kidney; and (2) it provides a means of objectively appraising the validity of clearance values obtained from the diseased kidney.* Finally, because the combined bilateral nephron population must always exceed 50 per cent of the original number, urea levels are maintained near the normal, and other chemical and physiologic abnormalities characteristic of the uremic state are minimized. It thus becomes possible to study the diseased kidney in an essentially normal internal environment.

If the conventional view is correct, morphologic derangements of the persisting nephrons should result in abnormalities of function in the diseased kidney irrespective of the presence of an intact kidney or of the status of body fluids. However, if the intrinsic functional capacity is preserved, the capabilities of nephrons of the diseased kidney should remain comparable to those of the intact organ.

* This appraisal is permitted by analysis of: (1) the reproducibility of clearance values for the diseased kidney under steady-state conditions; (2) the patterns of change in the diseased kidney as compared with the normal kidney during changing experimental conditions; and (3) the relationship between clearance ratios (e.g., GFR/ERPF, GFR/Tm_{PAH}, etc.) for the diseased versus the normal kidney in serial studies under a variety of experimental conditions.

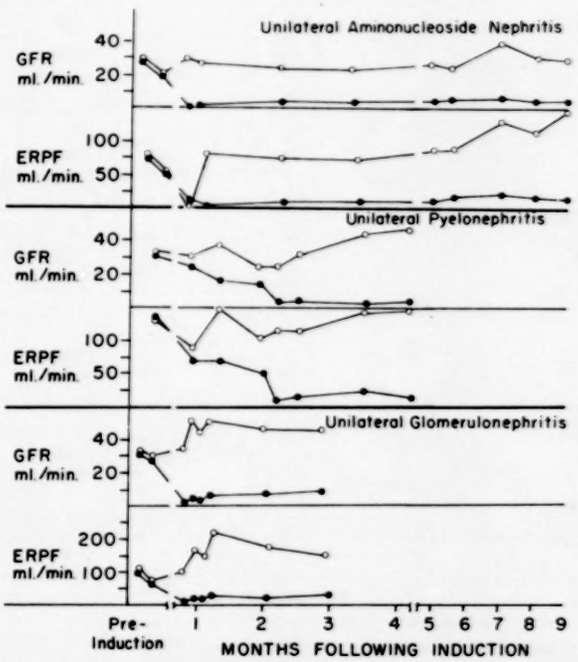


FIG. 1. Serial measurements of glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) for three representative dogs, each with a different type of unilateral renal disease. Closed circles = diseased kidney; open circles = normal kidney.

Three different forms of chronic renal disease have been studied: (1) a chemically induced lesion, aminonucleoside-nephritis [*18*]; (2) anti-kidney serum glomerulonephritis [*19*]; and (3) pyelonephritis [*20*]. All three lesions resulted in marked contraction of the renal mass and in severe architectural distortion of the persisting nephrons. The variation in the site of the nephron principally involved and in the extent of involvement created a spectrum of anatomic derangements analogous to that seen in the various forms of chronic Bright's disease.

The induction of disease, irrespective of the type, was associated with an absolute decrease in values for all renal functions in the experimental kidney. A representative set of measurements of glomerular filtration rate and renal plasma flow in three dogs, each with a different form of renal disease, is shown in Figure 1. The decrease in values implies that the number of functioning nephrons has decreased. The critical considerations, however, concern the functional capacity of the remaining nephrons. The experimental observations which have a direct bearing on this issue are presented in the following paragraphs.

The Relationship Between Glomerular and Tubular

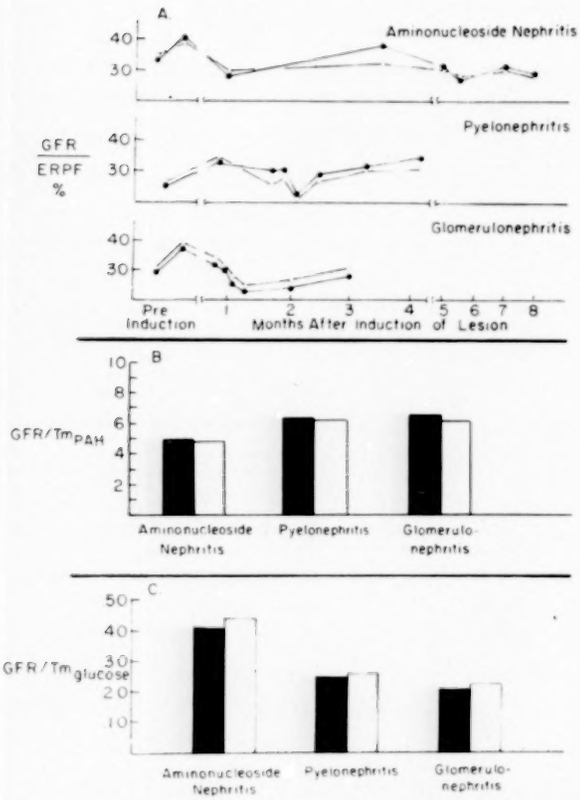


FIG. 2. Closed circles and bars = diseased kidney; open circles and bars = normal kidney. A, serial measurements of filtration fractions for the separate kidneys of three individual dogs. B, the ratio of GFR to Tm_{PAH} for normal and diseased kidneys of three representative dogs. C, GFR/$Tm_{glucose}$ ratios for three dogs, each with a different type of unilateral renal disease.

Function in the Diseased Kidney. It has frequently been contended that the residual nephrons of the diseased kidney may include (1) units in which the glomeruli are largely destroyed but in which the tubules retain functional ability (aglomerular tubules) and (2) units in which the glomeruli have normal filtering capacity but are attached to damaged tubules that serve largely as conduits which transport the glomerular filtrate in an essentially unmodified form into the urine (atubular glomeruli). That neither of these anomalies exists in the diseased kidney in the experimental animal is suggested by the following observations in which the relationships between glomerular and tubular function in the diseased organ are contrasted with those in the intact kidney.

Filtration fractions: The filtration fraction provides a measurement of the volume of glomerular filtrate formed per unit of effective renal plasma flow. If there is a detectable population of relatively aglomerular tubules in the diseased kidney, filtration fractions will be less for the diseased than for the intact kidney. Conversely an appreciable number of atubular glomeruli would result in abnormally high filtration fractions for the diseased organ.

In Figure 2A serial measurements of filtration fractions are shown for three representative dogs with unilateral renal disease. The values for the diseased kidneys are compared with those simultaneously obtained for the intact organs over periods up to eight months. The comparability of values for the individual kidneys of each dog, at any given time, is striking. This observation is inconsistent with the presence of an appreciable number of anomalous nephrons.

GFR/Tm_{PAH} ratios: The secretion of para-aminohippurate (PAH) occurs in the proximal tubule and is limited by a maximal rate of transport (Tm_{PAH}) [*5*]. By comparing glomerular function (GFR) with Tm_{PAH} it is possible to examine a functional relationship between glomeruli and their attached tubules.

In Figure 2B the ratios of glomerular filtration rate to Tm_{PAH} are shown for the diseased and normal kidneys of three representative dogs. The values for the individual kidneys of each dog are essentially equal. These observations indicate that the relationship of the filtering capacity to the tubular secretory capacity is the same in the nephrons of the diseased kidney as in those of the normal kidney. This, then, represents another point in evidence against the existence of anomalous nephrons.

GFR/Tm glucose ratios: The maximum rate of glucose reabsorption may also be employed as a reflection of tubular function, and the ratio of GFR to $Tm_{glucose}$ provides another means of comparing glomerular with tubular function. In Figure 2C ratios for GFR/$Tm_{glucose}$ are shown for the separate kidneys of three dogs with unilateral renal disease. In each instance the values for the normal and diseased kidney are essentially the same. These data thus provide additional evidence against the anomalous nephron thesis.

The Homogeneity of the Nephron Population in the Diseased Kidney. It has long been contended that the morphologic changes in the residual nephrons of the diseased kidney convert a relatively homogeneous population of nephrons into a heterogeneous group characterized by a spectrum of functional disorders [*26,27*]. One

method for evaluating the homogeneity of the nephron population consists of the measurement of glucose excretion during progressively rising plasma glucose concentrations [*28,29*]. The rationale for employing this technic, the glucose titration curve, in the dog with unilateral renal disease is as follows: If there is a greater degree of heterogeneity in the diseased kidney than in the normal organ discrepancies should emerge in the respective patterns of glucose excretion. In nephrons with normal glomeruli and impaired proximal tubules, filtered glucose should be poorly reabsorbed and glucose should appear in the urine at relatively low plasma concentrations. Conversely, in nephrons with damaged glomeruli but normal tubules (hence a decreased GFR/nephron) the amount of filtered glucose might remain less than the reabsorptive threshold of the attached tubules until extremely high plasma concentrations are obtained. Glucose reabsorption would then continue in the diseased kidney long after the Tm for the normal organ had been reached. The simultaneous existence of both forms of abnormal nephrons could also be detected. Glucose would appear in the urine of the diseased kidney before it does in that of the normal kidney, and glucose reabsorption would continue in the diseased kidney after the threshold had been reached for the intact organ.

Glucose titration curves have recently been obtained for animals with unilateral renal disease [*23*]. In Figure 3A a representative glucose titration curve is shown for a dog with a severe renal lesion in one kidney. Glucose concentrations were gradually increased from 120 mg. per cent to 840 mg. per cent. It may be seen that glucose reabsorption was complete in the diseased as well as in the intact kidney until the respective Tm's were reached. Moreover, once the filtered load of glucose exceeded the Tm level, no increment of glucose reabsorption occurred in either kidney. Finally, it may be seen (Fig. 3B) that Tm was reached at essentially the same plasma glucose concentration in the diseased as in the normal kidney.

These results lend strong support to the "intact nephron hypothesis." The inability to demonstrate any degree of functional heterogeneity in the diseased kidney suggests that nephrons which are markedly damaged may be lost from the population of functioning nephrons, whereas nephrons that continue to operate retain a remarkably uniform relationship between glomerular and tubular function. To evaluate further the integrity of the persisting nephrons of the diseased kidney a number of other parameters of function must be examined.

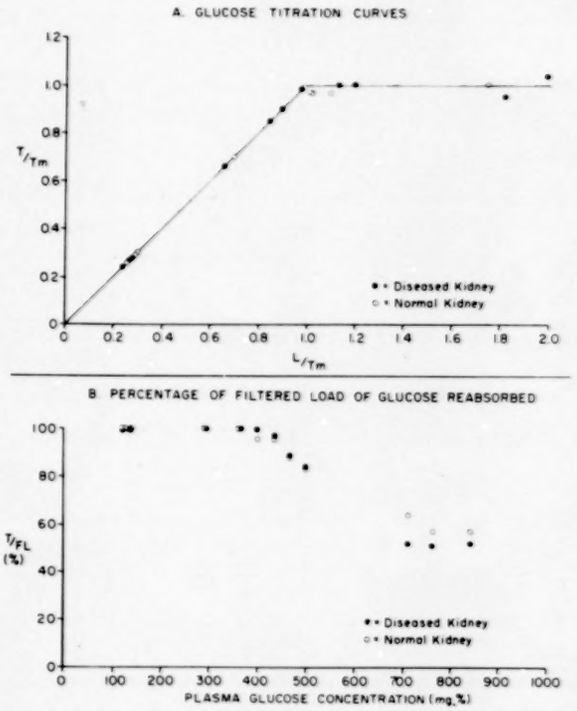


FIG. 3. A, glucose titration curves for the diseased and normal kidneys of a representative dog with unilateral glomerulonephritis. "T" refers to the rate of tubular reabsorption of glucose and "L" to the filtered load of glucose. Both terms have been factored by the respective Tm values for the separate kidneys. The reabsorption of glucose is complete by both kidneys until the load is equal to the Tm, following which reabsorption remains essentially constant. B, the percentage of filtered load of glucose which is reabsorbed is plotted against the plasma glucose concentration in milligrams per cent. Both kidneys reabsorbed 100 per cent of the filtered glucose until the load approximated the Tm, following which an increasing fraction of the filtered glucose was excreted bilaterally. It may be noted that the excretion of glucose into the urine began at approximately the same plasma glucose concentration in both kidneys.

Concentration and Dilution. Loss of the ability to concentrate the urine followed ultimately by impaired ability to dilute the urine are among the most characteristic features of chronic Bright's disease. These apparent abnormalities in renal function have long been attributed to destruction of the tubular sites for the concentrating and diluting operations. However, no experimental confirmation for this thesis has appeared, and there now are certain considerations that render the explanation open to question.

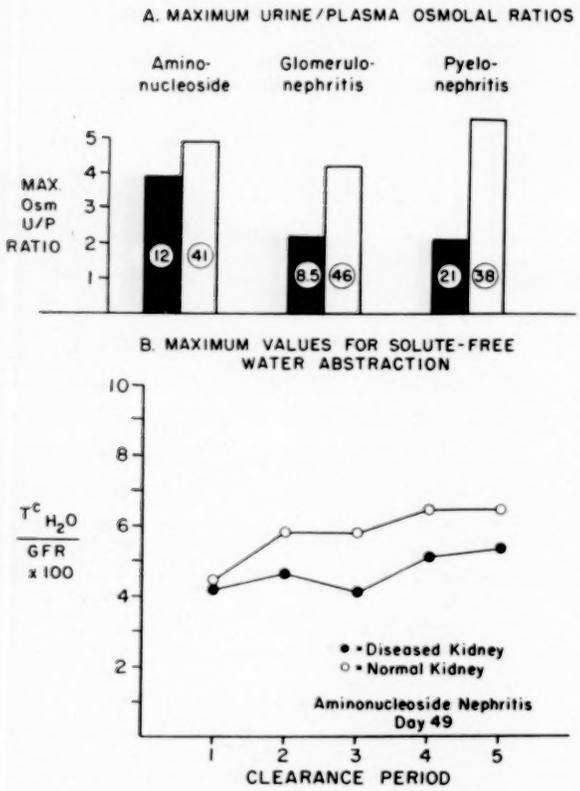


FIG. 4. A, maximum urine/plasma osmolal ratios obtained following fourteen hours of hydropenia. The black bars designate the diseased kidney; the open bars the normal kidney. The figures encircled in the bars represent the values for glomerular filtration rate for the individual kidneys. B, the volumes of solute-free water abstracted per 100 ml. of glomerular filtrate during the infusion of mannitol and Pitressin are shown for the diseased and normal kidneys of a representative animal.

Recent observations by Wirz [*30*], Berliner and co-workers [*31*], and Gottschalk and Mylle [*32*] have demonstrated that the production of a concentrated urine in the normal kidney depends upon (1) the elaboration of a hypertonic fluid in the medullary interstitial spaces by the reabsorption of solute (principally sodium) in the loop of Henle; (2) the diffusion of water out of the distal convolution, under the influence of ADH, resulting in an isotonic urine entering the collecting duct; and (3) the subsequent diffusion of water across the collecting duct into the hypertonic medullary interstitium. The vasa recta also play an important role in the concentrating mechanism. By virtue of a counter-current exchange operating between the two limbs of the hairpin capillary loop, the effective medullary blood flow is markedly diminished and dissipation of the hypertonicity of the interstitium by exchange with the plasma is thereby minimized. Osmotic equilibrium is ultimately established between the vasa recta, the medullary interstitial fluid and the urine in the collecting duct. The production of a dilute urine, on the other hand, appears to be dependent simply upon (1) the reabsorption of solute in the loop of Henle and distal convolution and (2) the limited permeability to water of the distal convolution and collecting duct in the absence of ADH. The reabsorption of solute without proportional back-diffusion of water results in a hypotonic urine.*

Theoretically, the impaired ability to concentrate and dilute the urine in chronic Bright's disease could result from anatomic derangement of any of the constituent parts of the respective mechanisms. However, it is also possible that functional adaptations in *intact nephrons* may be largely responsible for the evolution of isosthenuria in chronic bilateral renal disease. Recent experimental observations have been obtained which support the latter possibility [*21,22*]. These data are summarized in the following paragraphs.

Concentrating capacity: When the animal with unilateral renal disease is deprived of water the diseased kidney is capable of elaborating urine distinctly hypertonic to plasma. In Figure 4A values for the maximal urine/plasma osmotic ratio are shown for the individual kidneys of three representative dogs. In each instance the diseased kidney retained the ability to concentrate the urine, although the values were less than those for the intact organ. The concentrating capacity may also be examined during high rates of solute excretion induced by osmotic diuresis. Under these conditions the volume of water abstracted from the urine in excess of the isotonic equivalent of solute (i.e., solute-free water or $T^c_{H_2O}$) serves as a measure of the efficiency of the concentrating mechanism. In Figure 4B maximum values for solute-free water abstraction are shown for diseased and intact kidneys of a representative dog during infusion of mannitol and Pitressin.® The values for the diseased kidney, expressed as milliliters of solute-free water abstracted per 100 ml. of GFR ($T^c_{H_2O}$/GFR), are within the normal range and, moreover, are only slightly less than the simultaneous values obtained for the intact

* A detailed review of these concepts may be found in a recent paper by Smith [*33*].

organ. These observations suggest that the basic integrity of the concentrating mechanism in the diseased kidney is preserved, and thus provide evidence against significant anatomic disruption of the constituent parts. This conclusion receives further support from studies, to be cited subsequently, that indicate that the differences between the two kidneys relate in large part to reversible functional adaptations.

Recent studies by Baldwin and co-workers [*34*] provide evidence that the concentrating mechanism in man is not destroyed by a progressive renal lesion. In patients with chronic bilateral renal disease, the infusion of mannitol and Pitressin revealed values for $T^c_{H_2O}/GFR$ which were frequently within the normal range. In the two patients with the most severe renal disease (as evidenced by the lowest values for glomerular filtration rate) the values for $T^c_{H_2O}$ were 3.8 and 6.1 ml. per 100 ml. of glomerular filtrate. In several of the patients the values for solute-free water abstraction were below the normal range. However, as will be discussed subsequently, this does not necessarily imply that the intrinsic capacity of the concentrating mechanism was destroyed.

Diluting capacity: In Figure 5A the values for minimum osmotic urine/plasma ratios are shown for the diseased and normal kidney of three representative dogs with unilateral renal disease. The diluting ability of the diseased kidney, as judged by this parameter, was at least equal to the normal kidney, and in many instances the diseased kidney elaborated a more dilute urine than the normal organ. In Figure 5B the maximum ability to elaborate solute-free water (i.e., free water clearance or C_{H_2O}) is shown for the diseased and normal kidneys of a representative dog. Values for the diseased kidney, expressed as free water clearance per 100 ml. of glomerular filtrate (C_{H_2O}/GFR), are not only within the normal range but also exceed the simultaneous values for the normal organ. Recent observations by Kleeman and co-workers have confirmed the existence of normal values for C_{H_2O}/GFR in human subjects with bilateral renal disease [*35*].

The foregoing observations are consistent with the thesis that the concentrating and diluting mechanisms are inherently intact in the nephrons of the diseased kidney. The development of a diminishing ability to alter the tonicity of the urine in bilateral renal disease may therefore be related principally to functional

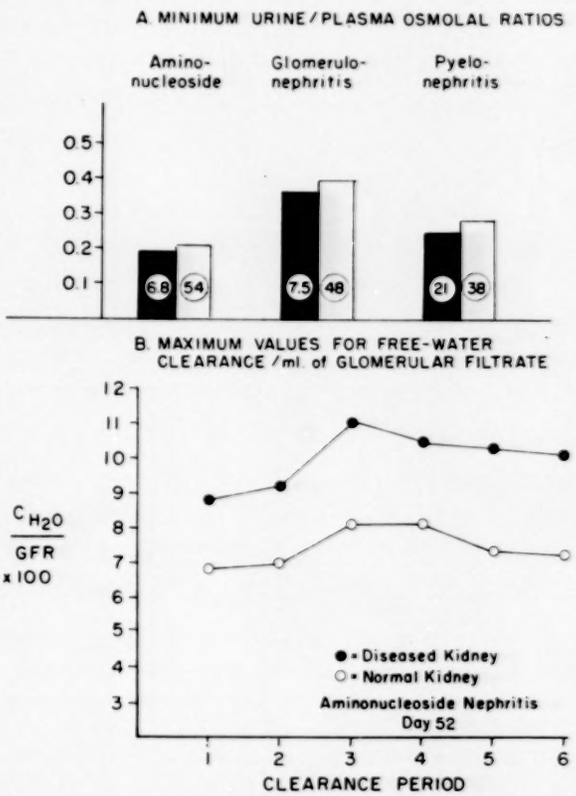


FIG. 5. A, minimum urine/plasma osmolal ratios following the administration of 50 to 70 ml./kg. of water and 5 ml. of absolute alcohol. The values for the diseased kidney are shown in solid bars and those for the intact kidney in open bars. Values encircled in the bars represent glomerular filtration rates for the individual kidneys. B, maximum values for free-water clearance per 100 ml. of glomerular filtrate are shown for the diseased and intact kidneys of a representative dog following water loading and alcohol administration.

changes rather than to anatomic abnormalities of the residual nephrons. In considering the possible nature of these functional changes, one essential concept must be established: *A decreasing ability to concentrate and dilute the urine does not necessarily imply that the concentrating and diluting operations are impaired.* It is quite possible for the urine to have a *relatively* fixed osmolality (or specific gravity) in the presence of normally functioning concentrating and diluting processes if the volume of urine passing the active sites is large. This concept is illustrated in the following paragraph.

During conditions that promote maximum concentration (i.e., hydropenia or administration of Pitressin) the urine entering the collecting ducts is thought to be isotonic to the plasma [*36*]. From this isotonic solution water back-diffuses into the hypertonic medullary interstitium only

until the urine comes into osmotic equilibrium with the medullary interstitial fluid. When the amount of urine flowing through the collecting ducts is small, as it typically is when there are 2 million nephrons sharing a normal excretory load, osmotic equilibrium is achieved after the back-diffusion of a minimal quantity of water, and the urine will be highly concentrated. However, when the volume of isotonic urine reaching the collecting ducts is large, increasing volumes of solute-free water will diffuse into the medulla, and osmotic equilibrium will occur at a lower osmolality. The larger the volume of water diffusing into the interstitial fluid, the lower will be the osmolality of the final urine.* *Thus, the greater the rate of urine flow entering the collecting ducts, the less the concentration of the final urine will deviate from that of the plasma despite the continued and efficient operation of the concentrating mechanism.*† In chronic Bright's disease a diminished number of nephrons may continue to excrete a normal solute load. This is accomplished by the excretion of a greater than normal fraction of the glomerular filtrate by each residual nephron. (On a given solute intake, the fewer the number of surviving nephrons, the greater is the fraction of glomerular filtrate excreted by each if balance is maintained.) Thus, despite the continuing activity of the concentrating mechanism, the high rates of urine flow through the collecting ducts would militate against the elaboration of highly concentrated urine.

With respect to the diluting capacity, high rates of solute flow per nephron will also diminish the degree to which the final urine may be diluted. During low rates of solute excretion, in the normal kidney, the reabsorption of solute without equivalent amounts of water may result in a markedly dilute urine. However, when the flow rate per nephron increased (as in chronic Bright's disease), abstraction of the same amount of solute from a considerably larger volume of urine will result in a far smaller decrease in final urine osmolality.

The high rate of solute excretion per residual nephron, in bilateral renal disease, also provides a partial explanation for the fact that the ability to concentrate the urine decreases before the ability to dilute the urine. The osmolality of the maximally concentrated urine in man is approximately 1200 mOsm/L., whereas the osmolality of a maximally dilute urine is approximately 40 mOsm/L. Hence, with a plasma osmolality of 300 mOsm/L., the concentrated urine increases by 900 mOsm/L., but the diluted urine decreases by only 260 mOsm/L. A 50 per cent reduction in range on both sides of isosmolality imposed by an increased rate of urine flow past the concentrating and diluting sites would therefore *appear* to represent a much greater defect in concentrating ability than in diluting ability.

The progressive restriction in the range over which the urine osmolality may be varied in chronic Bright's disease may thus be related in large part to an increased rate of solute excretion per nephron. That there may be additional factors contributing to the loss of the ability to concentrate the urine in bilateral renal disease in man is suggested by certain observations on dogs with unilateral renal disease.

It has already been noted that during osmotic diuresis the values for $T^c_{H_2O}/GFR$ were slightly less for the diseased than for the normal organ. During all experiments of this nature the diseased kidney excreted a greater fraction of its filtered solute than did the normal kidney. In accordance with the concepts discussed, the greater the rate of solute excretion, the lower will be the osmolality of the final urine. Comparison of the urine osmolality of the diseased kidney with the concurrent values of the normal kidney does indeed demonstrate lower values for the diseased organ [*22*]. However, if the urine of the diseased kidney comes into osmotic equilibrium with the medullary interstitial fluid, the excretion of a greater fraction of filtered solute should result in the abstraction of *more solute-free water* in the nephrons of the diseased kidney than in those of the normal kidney. The fact that $T^c_{H_2O}/GFR$ was less for the diseased than for the normal organ must therefore be explained. In part, this discrepancy may be related to the fact that the GFR per residual nephron in the diseased kidney may be slightly greater than the GFR per nephron in the normal kidney. (This will be discussed more fully in the section on *Functional Adaptations in the Persisting Nephrons.*) A greater value for GFR per nephron

* This concept has been discussed in more detail by Berliner and co-workers [*31,37*].

† This phenomenon may be demonstrated in the normal subject during experimentally induced osmotic diuresis [*38–40*]. The greater the rate of urine flow, the less concentrated is the final urine (i.e., the closer the osmolality approaches that of the glomerular filtrate) although the removal of solute-free water continues at an increasing rate.

would decrease the absolute value for the derived ratio $T^c_{H_2O}/GFR$. This does not appear to provide a complete explanation, however, particularly in view of the fact that values for C_{H_2O}/GFR have been invariably *greater* for the diseased than for the normal kidney. Several additional possibilities may be considered in explanation of these observations: (1) The abstraction of sodium by the loops of Henle in the diseased kidney may be less than the simultaneous values for the normal organ. Recent observations, however, suggest that this is unlikely [*25*]. (2) The urine from the diseased kidney may not come into osmotic equilibrium with the medullary interstitium, due to impaired permeability of the collecting ducts or to subtle distortion of the spatial relationships between the collecting ducts, medullary interstitium and vasa recta.* (3) The degree of hypertonicity established in the medulla of the diseased kidney may be less than that of the normal kidney, due to a relatively greater medullary blood flow in the diseased organ. Berliner and co-workers [*31*] have postulated that the concentration of the medullary interstitial fluid is inversely proportional to the square of the blood flow through the vasa recta. Although no means are currently available for measuring vasa recta blood flow, indirect evidence suggests that the medullary flow be increased in the diseased kidney.†

The greater values for C_{H_2O}/GFR for the diseased than for the normal kidney may also be explained on a functional basis. During low rates of solute excretion the sodium-reabsorbing sites in the distal tubules may be operating at less than capacity. The delivery of more sodium to the distal segments of the diseased kidney than to those of the contralateral normal organ would permit greater solute reabsorption per nephron, and hence the elaboration of more osmotically unobligated water per nephron. During high rates of solute excretion, in the absence of ADH, greater values for C_{H_2O}/GFR for the diseased kidney may have another explanation. In patients with diabetes insipidus, Orloff and associates [*41*] have shown that increasing rates of solute excretion (induced by infusion of mannitol) will increase free-water clearance. It has been suggested that the distal convolutions and perhaps the collecting ducts are permeable (although to a limited degree) to water, even in the absence of ADH, and that the greater the flow rate through these segments the less will be the water lost by back-diffusion. In the patient with bilateral renal disease the persistence of high rates of solute excretion could, according to this mechanism, tend further to preserve diluting ability after the ability to concentrate the urine is markedly impaired.

Summary of Data Relating to the Concentrating and Diluting Mechanisms of the Diseased Kidney. The observations on the animals with unilateral renal disease suggest that the concentrating and diluting mechanisms remain essentially intact in the nephron of the diseased kidney. This provides evidence against the thesis that anatomic disruption of residual nephrons in the diseased kidney is the primary factor responsible for the limited ability to concentrate and dilute the urine in bilateral renal disease. The latter limitations, therefore, may be provisionally attributed to functional adaptations occurring in the persisting nephrons. Presumably, the fewer the number of remaining nephrons, the more advanced these adaptive changes are. The major adaptation consists of a greater rate of solute excretion per nephron. This would tend to diminish the maximum range of osmolality on either side of the plasma value, and would thus contribute to the emergence of relative isosthenuria. In addition, the possibility has been considered that in the kidney with a diminished population of nephrons the degree of hypertonicity achievable in the medullary interstitial fluid is restricted, and one mechanism proposed for this is an increase in vasa recta blood flow. This would further diminish the maximal achievable osmolality of the urine. The increased flow rate per nephron in the diseased kidney might tend to diminish the limited back-diffusion of water occurring in the absence of ADH, and this would contribute to the continu-

* Preliminary observations indicate that this also is unlikely. Thus studies on animals with a unilateral hemi-infarcted kidney (in which the residual nephrons are uninvolved by a progressive renal lesion) reveal the same differences in urine osmolality, $Tc^e_{H_2O}/GFR$, etc., between the hemi-infarcted and normal kidneys as exist between diseased and normal kidneys. However, it is conceivable that alterations in spatial relationships in the inner medulla may be of somewhat more importance in man than in the dog in view of the fact that the human kidney has fewer long loops of Henle than the dog kidney.

† The available evidence is consistent with the hypothesis that GFR per nephron is increased in the diseased kidney. Moreover, renal plasma flow per nephron may also be increased, inasmuch as the filtration fractions for the diseased kidney generally are equal to those of the normal kidney. (Fig. 2A). Thus an increase in total renal plasma flow per nephron may conceivably be associated with an increase in vasa recta blood flow.

ing ability to dilute the urine after the ability to concentrate the urine is severely impaired.

There is one clinical observation that would seem to be at variance with the thesis that the concentrating mechanism remains intact in the nephrons of the diseased kidney. In the presence of far advanced renal failure in man it rarely has been possible to demonstrate the production of a hypertonic urine, despite prolonged water deprivation and infusion of Pitressin.* There are certain theoretical and experimental observations that suggest that the concentrating mechanism may continue to operate under these conditions. Theoretically, the possibility exists that when the population of functioning nephrons is markedly diminished, the flow rate through each nephron is so brisk that the time for water diffusion out of the tubule is inadequate to permit the delivery of an *isotonic urine* to the collecting ducts. Were the urine reaching the collecting ducts to be hypotonic, removal of solute-free water by the concentrating mechanism might continue and yet not result in a final urine more concentrated than the plasma. Preliminary experimental observations support this contention. Zak, Brun and Smith [*40*] have suggested that the urine leaving the distal convolution might remain hypotonic in normal humans subjected to massive osmotic diuresis. In addition, Raisz and associates [*43*] have found that values for $T^c_{H_2O}$ *decrease* toward zero when more than 30 per cent of the glomerular filtrate is excreted. In the dog with unilateral renal disease, massive osmotic diuresis has been found to result in the elaboration of a *hypotonic urine* by the diseased kidney, despite the continuous infusion of Pitressin [*44*]. Figure 6 depicts this phenomenon in an animal with a severely diseased kidney, using the stop-flow technic of Malvin, Wilde and Sullivan [*45*]. During the infusion of mannitol and Pitressin the urine became persistently hypotonic. Following three conventional clearance periods, the ureter of the diseased kidney was occluded for a period of four minutes. During this time the urine presumably remained static in the functioning nephrons while the tubular transport mechanisms continued to act upon the intratubular fluid. Following the four-minute interval of stop-flow the ureteral clamp was suddenly released and multiple small samples of urine were obtained over a period of ninety seconds. During the stop-flow interval, the hypotonic urine became hypertonic in the region of the collecting duct. With reinstitution of free-flow, the urine again became hypotonic. It thus appears that hyposthenuria may occur in a diseased kidney subjected to extreme osmotic diuresis despite the continuing operation of the concentrating mechanism. It may be reiterated that under steady-state conditions the patient with advanced bilateral Bright's disease may excrete a fraction of his glomerular filtrate as great as that induced experimentally by infusion of mannitol [*46*].

The thesis that the concentrating and diluting processes continue to operate in the surviving nephrons of the diseased kidney provides a rational explanation for the long-standing observation that the patient with chronic Bright's disease may maintain constant tonicity of the body fluids despite unrestricted water intake. Were the concentrating and diluting mechanisms to be impotent and the urine to have a rigidly fixed osmolality at all times, water excretion would be determined exclusively by the total solute excretion, and the water lost in the urine would bear little or no relationship to the concurrent rate of water intake. The responsibility for maintaining the tonicity of body fluids would therefore devolve entirely upon the thirst mechanism. However, it is well known that variation in water intake in the uremic patient does evoke changes in urine volume that are independent of solute excretion [*13*]. This may readily be explained if the concentrating and diluting mechanisms of the functioning nephrons retain functional capacity.

Patterns of Sodium Excretion. The uremic patient typically retains a remarkable ability to regulate sodium excretion in accordance with intake and body needs. This is attested to by the persisting capacity to maintain sodium balance (and normal plasma sodium concentrations) despite the presence of far advanced renal disease.* Although the range of sodium excretion is restricted in the uremic patient when compared to the normal subject (i.e., neither a sodium-free urine nor excessive quantities of urinary sodium may ordinarily be excreted), the

* Bradley [*42*], however, has noted that patients with far advanced renal disease may elaborate a highly concentrated urine following the onset of congestive heart failure. Presumably the heart failure was associated with a diminished filtration rate and a diminished solute load.

* Platt has commented on this phenomenon in some detail [*11*].

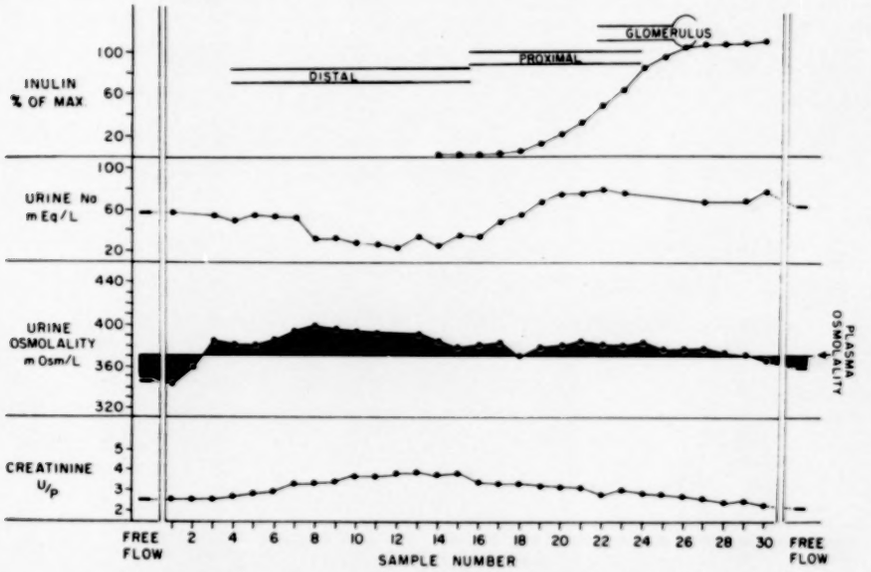


FIG. 6. Stop-flow experiment on the diseased kidney of an animal with unilateral glomerulonephritis. The individual bars to the far left were obtained during free flow prior to occlusion of the ureter. The points between the vertical lines represent successive samples of urine obtained immediately after four minutes of stop-flow. The values to the left represent those from the distal portions of the nephrons, whereas those to the right represent those obtained from the more proximal segments. The solid bars to the far right represent free flow samples after completion of the small sample collections. Creatinine U/P = creatinine urine/plasma ratios. The experiment was performed during the infusion of mannitol (12.5 per cent solution) at the rate of 8 ml./minute and Pitressin (75 milliunits prime and 1 milliunit/minute in the sustaining solution). It may be seen that despite the continuous infusion of Pitressin the urine was hypotonic prior to the initiation of stop-flow. However, during the period of stop-flow the urine became *hypertonic* in a distal portion of the nephron. Subsequent to reinstitution of free flow, the urine once again became hypotonic. These data suggest that during free flow periods, the urine was hypotonic despite the continuing operation of the concentrating mechanism. Presumably the urine presented to the concentrating site was hypotonic rather than isotonic.

patient with chronic Bright's disease can increase sodium excretion when salt intake increases and decrease it when salt intake decreases. Moreover, during experimental lowering of GFR [*47*] and in certain clinical circumstances associated with an acute decrease in filtration rate (e.g., marked contraction of extracellular fluid volume or congestive heart failure) and therefore a decreased filtered load of sodium presented to each functioning nephron, the uremic patient may temporarily regain the ability to reabsorb virtually all the filtered sodium.

The capacity so to regulate sodium excretion suggests that the sodium transport systems in the remaining nephrons are basically intact and respond in an appropriate manner to extrarenal stimuli. Random and chaotic destruction of intrinsic tubular processes would be expected to result in unpredictable patterns of salt excretion that would be poorly integrated with either the salt intake or the needs of the organism.

The inability of the patient with bilateral renal disease to decrease sodium excretion as effectively as the normal subject has frequently been accepted as evidence that sodium transport mechanisms in the tubule are impaired by the underlying pathologic process [*48*]. Were this true, the diseased kidney, whether it exists in a normal or a uremic environment, should be unable to excrete urine extremely low in sodium. In Figure 7 sodium excretion, during sodium deprivation, is shown for the diseased and intact kidneys of two dogs with severe unilateral renal disease. The total amount of sodium excreted by the diseased organs was less than 2 mEq. per day, suggesting that the nephrons of the diseased kidneys were capable of conserving sodium with extreme efficiency. Moreover, dur-

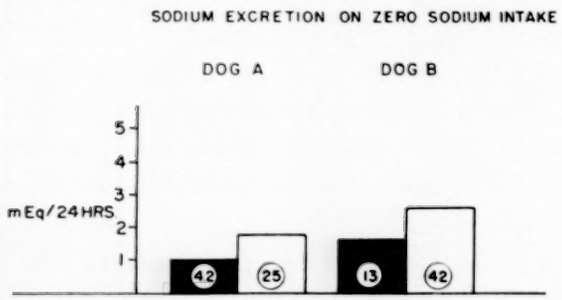


FIG. 7. Sodium excretion on a sodium-free diet in two representative dogs. The values for the diseased kidney are shown in solid bars and those for the intact kidney in open bars. Values for GFR are shown encircled in bars.

ing mannitol diuresis, occlusion of the ureter of the diseased kidney for four minutes (stop-flow experiments) was associated with the delivery of urine virtually free of sodium from the region of the distal tubule [*25*]. These phenomena could not occur if even a small percentage of the functioning nephrons was incapable of reabsorbing sodium.

Sodium excretion by the diseased kidney has also been studied during conditions which promote natruresis [*25*]. During osmotic diuresis induced by the intravenous infusion of mannitol, urea, glucose, phosphate and PAH, the rates of sodium excretion increased in the diseased kidney in a manner which paralleled that seen in the normal kidney. During the infusion of hypertonic sodium chloride the diseased kidney manifested the ability to increase sodium excretion in a manner comparable to that of the intact organ. Following the administration of a mercurial diuretic the diseased kidney retained the ability to increase sodium excretion rates. Finally, in association with expansion of extracellular fluid volume, sodium excretion rates increased in the diseased kidney in a manner which paralleled that noted in the intact organ.

The patterns of chloride excretion by the diseased kidney were similar to those of sodium, suggesting that the residual nephrons retained the capacity both to decrease and increase chloride excretion in response to the appropriate stimuli.

Pattern of Potassium Excretion. The efficiency with which potassium balance is maintained in chronic Bright's disease has been discussed previously. In order to accomplish this in the face of a normal dietary intake, each remaining nephron must be capable of excreting quantities

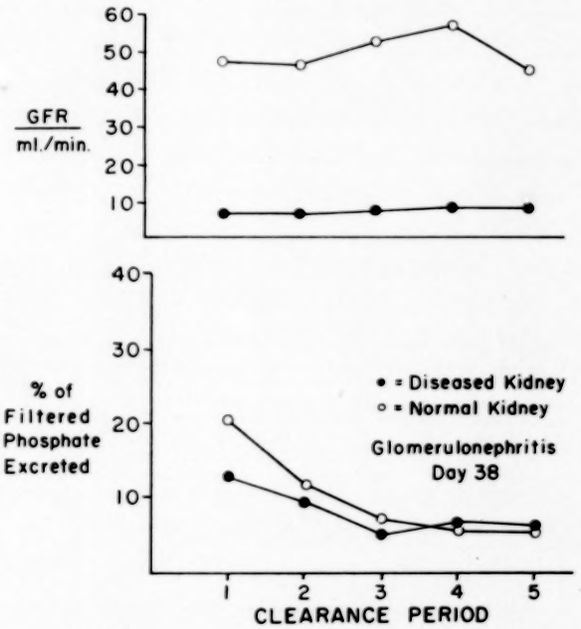


FIG. 8. Phosphate excretion by the diseased and normal kidneys of a representative dog. In the top graph, values for GFR for the respective kidneys are shown. In the bottom graph, the percentage of filtered phosphate excreted by the diseased and normal kidneys is shown.

of potassium considerably in excess of those ordinarily excreted by the nephrons of normal kidneys.

Values for potassium clearance in excess of those for GFR (i.e., active secretion of potassium) for the diseased kidney in man have frequently been recorded [*49,50*]. Preliminary observations in animals with unilateral renal disease indicate that the patterns of potassium excretion, under varying experimental conditions, are generally comparable to those simultaneously observed in the intact organ [*44*]. These data are consistent with the thesis that the mechanisms for potassium excretion are intact in the surviving nephrons of the diseased kidney.

Phosphate Excretion. It has been noted previously that during progressive renal failure, phosphate reabsorption by the diseased kidney diminishes, thereby augmenting the ability of a decreasing nephron population to maintain phosphate balance. That this decrease represents a homeostatic change and is not the result of fortuitous impairment of the ability of the tubules to reabsorb phosphate is indicated by examination of the simultaneous pattern of phosphate reabsorption by the diseased and intact kidneys of the experimental animal with unilateral renal disease [*24*]. In Figure 8

phosphate excretion is shown for the individual kidneys of a representative dog with a severe unilateral renal lesion. The fraction of filtered phosphate which is reabsorbed is essentially the same for the diseased kidney as it is for the intact organ. The comparability between diseased and intact kidneys persisted during experimental conditions which modify phosphate reabsorption (e.g., PAH and glucose loading), and during phosphate loading.

Regulation of pH. The ability of the persisting nephrons of the diseased kidney to maintain hydrogen ion balance also appears to increase adaptively as the disease advances. Although acidosis invariably occurs during the course of chronic Bright's disease, it does not progress inexorably and there are long periods when pH is maintained constant [*51,52*]. Presumably the stabilization of pH, even though it occurs at an acidotic level, is a reflection of the capacity of the residual nephrons to increase hydrogen ion transport sufficiently to maintain excretion equal to acquisition. Studies are now in progress to evaluate this concept further.

The Excretion of Glucose. Impairment of glucose reabsorption in even a few of the functioning nephrons of the diseased kidney would result in glycosuria at relatively low plasma glucose levels. Evidence has already been cited to show that in the animal with unilateral renal disease the pattern of glucose reabsorption by the nephrons of the diseased kidney is identical with that of the normal kidney. Moreover, in the non-hyperglycemic patient with chronic Bright's disease the urine remains singularly free of glucose.

The Excretion of Amino Acids. The tubular reabsorption of filtered amino acids at normal plasma levels is essentially complete in the intact kidney. Recent studies by Lathem and coworkers [*53*] indicate that amino acid reabsorption remains unimpaired in the patient with chronic Bright's disease. The continuing ability to extract a high percentage of the amino acids from the glomerular filtrate demands a normal degree of efficiency from virtually all functioning nephrons.

THE DISSOCIATION BETWEEN STRUCTURE AND FUNCTION IN THE DISEASED KIDNEY

In Figure 9 the separate kidneys of a dog with unilateral renal disease are shown; one kidney is normal, the other demonstrates the changes of severe experimentally induced glomerulonephritis. Microscopically, a wide spectrum of architectural changes was noted. Many of the glomeruli were completely replaced by fibrous tissue. In others, congestion was present, and in some the glomerular tufts were contracted. Proliferative changes were widespread. The glomeruli with no evident abnormalities varied in size from small to markedly enlarged. The tubules also showed a spectrum of pathologic changes ranging from normal architecture to complete destruction. Many of the tubules contained intraluminal casts. In the interstitial areas, hemorrhages and diffuse infiltration of mononuclear cells were noted. The composite picture presented may perhaps best be described by a quotation from Oliver [*26*]: "The processes of disease have resolved the architectural unity of the normal kidney into the complete and absolute disparity of thousands of independent different entities, the abnormal nephrons."

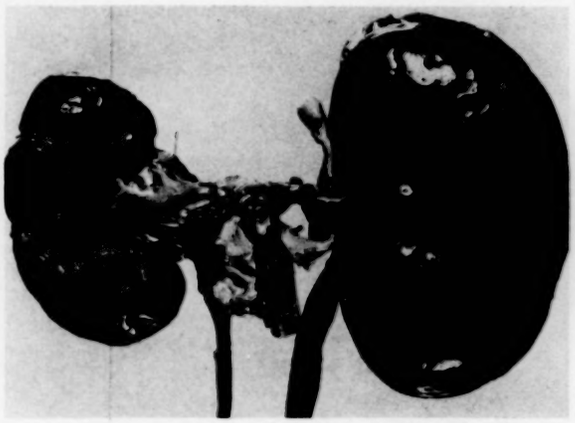


FIG. 9. The separate kidneys of an animal with experimentally induced glomerulonephritis are shown eighty-eight days after induction of the lesion.

In Table 1 the functional capacity of this diseased kidney is compared with the simultaneous functions of the contralateral normal kidney. The volume of glomerular filtrate formed per unit of renal plasma flow (filtration fraction) is essentially the same in the diseased as in the normal kidney. The relationship between filtration rate and the maximum ability to secrete PAH is comparable bilaterally. The ratio between glomerular filtration rate and maximum tubular reabsorption of glucose is the same bilaterally. If the plasma glucose concentration is increased (Fig. 3) glucose appears in the urine of both kidneys at the same plasma glucose concentration, and the glucose threshold (Tm) is reached simultaneously by both kidneys.

TABLE I
STUDIES ON THE DISEASED AND NORMAL KIDNEY OF AN ANIMAL WITH UNILATERAL GLOMERULONEPHRITIS*

Parameter	Day Following Induction	Diseased Kidney	Normal Kidney
GFR (ml./min.)	12	2.6	34.3
	81	9.4	45.9
Filtration fraction (%)	12	32.0	33.7
	81	28.3	30.1
GFR/Tm_{PAH}	81	6.51	6.14
$GFR/Tm_{Glucose}$	31	0.21	0.23
$T^c_{H_2O}/GFR(\times 100)$	17†	5.48	6.88
$C_{H_2O}/GFR(\times 100)$	38	8.15	4.61
% Filtered Na reabsorbed	17†	92.4	95.6
	66‡	94.0	93.8
% Filtered Cl reabsorbed	17†	90.8	94.3
	66‡	93.4	92.1
$\frac{U_K V}{FL_K}(\times 100)$	17†	66.9	43.9
	66‡	44.1	61.3
% Filtered phosphate reabsorbed	38	92.1	89.9
	66‡	85.6	81.1
% Filtered urea reabsorbed	38	47.1	49.5
	66	40.1	39.4

* The gross appearance of the kidneys at autopsy is shown in Figure 9. U_KV/FL_K is an expression for the excretion rate of potassium divided by the filtered load of potassium.
† Mannitol diuresis.
‡ Urea diuresis.

During the infusion of mannitol and Pitressin the concentrating mechanism of the diseased kidney functions at a level comparable to that of the normal organ. During water-loading and administration of alcohol the diluting capacity of the diseased kidney is superior to that of the normal organ. Sodium and chloride excretion by the diseased kidney is comparable to that of the intact organ. Potassium excretion by the diseased kidney does not differ in a consistent manner from that by the intact organ. The fraction of filtered phosphate excreted by the diseased kidney is comparable to that by the normal kidney. Finally, the fraction of filtered urea excreted by the diseased kidney is essentially the same as that by the normal kidney.

Thus there appears to be a remarkable discrepancy between the morphologic changes and the functional capacity of the diseased organ. The chaotic alterations of structure and the production of a morphologically heterogeneous population of nephrons is incontestable. However, the functional capacity of the diseased kidney is neither disorganized nor heterogeneous. Both in this dog and in all other animals studied to date, glomerular and tubular functions have remained orderly and predictable in the nephrons of the diseased kidney, and the capacity of the tubules to accomplish all of the functions examined is similarly orderly, predictable and, in most instances, essentially normal. The strange dissociation between the structural derangements and the functional capacity of the persisting nephrons of the diseased kidney permits the formulation of the following working hypothesis: *In chronic renal disease associated with marked nephron destruction, any nephron that sustains marked structural damage to any portion of its anatomy may be lost from the population of functional nephrons, whereas nephrons that continue to function largely retain their essential functional integrity.**

PHYSIOLOGIC ADAPTATIONS IN THE PERSISTING NEPHRONS

The preservation of normal function cannot by itself account for one of the major accomplishments of the diseased kidney, the ability to excrete normal amounts of salt and water despite a major reduction in the nephron population. In the kidney with only 10 per cent of the original number of nephrons there must be a tenfold increase in the excretion of salt and water by each nephron if balance is to be maintained on a normal diet.

The manner in which this functional adaptation is accomplished is not completely understood; however, at least two possibilities exist. The first, which has been considered by many authors [*11,13,15*], suggests that in the presence of uremia the high concentrations of urea in the glomerular filtrate promote a continuing osmotic diuresis analogous to that seen in the normal subject during infusion of urea (or mannitol). That there is some degree of osmotic diuresis in the patient with chronic Bright's disease and azotemia may be accepted provisionally. However, it does not seem likely that this is the only, or even the major, factor in the functional changes occurring in the diseased kidney. Thus in the animal with unilateral renal disease, maintained on a salt-free diet, the diseased kidney continues to reabsorb over 99 per cent of the filtered sodium, despite persistent elevation of plasma urea concentrations to levels seen in advanced uremia by exogenous urea loading [*44*].

The second possible adaptive change is a mechanistic one first alluded to in a general way by Fremont-Smith and associates [*54*] and later

* An alternative explanation is possible. This would imply that if glomerular or tubular function is suppressed in an individual nephron, there will be a simultaneous and proportional decrease in other functional systems in that nephron. This would demand autoregulation of glomerular-tubular balance capable of influencing multiple tubular transport systems.

amplified and extended by Platt [*11*]. This suggests that a compensatory increase occurs in the glomerular filtration rate of each residual functioning nephron. This hypothesis, although unproved, has much to recommend it. The ability of individual nephrons to exhibit a permanent increase in filtration rate in response to a decrease in total nephron population is well documented in compensatory hypertrophy following unilateral nephrectomy. In some instances the glomerular filtration rate of the remaining kidney may practically double over a period of weeks to months without any increase in the number of nephrons [*5*]. Similarly, in the experimental animal the removal of three-fourths of the renal mass is attended by a striking increase in filtration rate in the residual segment of kidney [*55*].

Some experimental evidence that is consistent with an adaptive increase in glomerular filtration rate in the surviving nephrons of the diseased kidney has recently been obtained [*44*]. In the animal with unilateral renal disease the patterns of function of the nephrons of the diseased kidney have been shown to parallel those of the normal kidney. However, under certain experimental conditions slight but consistent differences in function may be demonstrated. These are shown in a representative experiment (Fig. 10) in which osmotic diuresis was induced by infusion of mannitol and Pitressin. During four conventional clearance periods the diseased kidney excreted a larger fraction of its filtered solute and water than the normal kidney. The superiority of total solute excretion was largely due to the excretion of a greater fraction of the filtered sodium (and chloride). Two other differences were observed: (1) the concentration of sodium was *greater* in the urine of the diseased kidney and (2) the concentration of total solute (i.e., osmolality) was *less* in the urine of the diseased kidney. A larger volume of glomerular filtrate entering the nephrons of the diseased kidney than the intact kidney could theoretically account for all of these differences.* An attempt

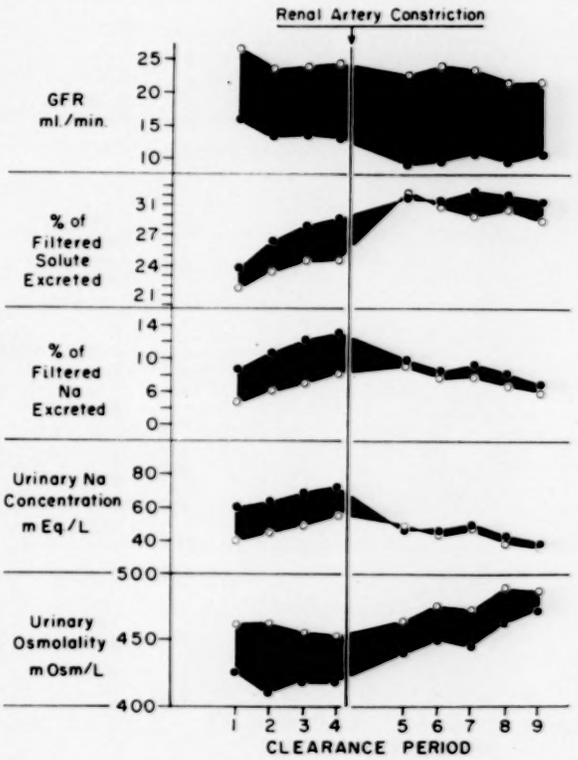


FIG. 10. Effects of acute experimental reduction in GFR of the diseased kidney (but not the normal kidney). Closed circles = diseased kidney. Open circles = normal kidney. The points to the left of the solid line were obtained prior to the compression of the renal artery of the diseased kidney. The points to the right of the line were obtained subsequent to compression of the artery.

to examine this thesis is shown in Figure 10. At the conclusion of the fourth clearance period the

* A greater volume of filtrate would result in a greater volume of urine entering each successive segment of the nephron. The reabsorption of salt and water might proceed isosmotically in the proximal tubules of both kidneys, but a larger volume would enter the loops of Henle of the diseased organ. As the urine courses through the loops of Henle, sodium reabsorption may occur at essentially the same rate in the nephrons of both kidneys, and in the distal tubules equivalent amounts of sodium may be reabsorbed bilaterally. If antidiuretic hormone effect is maximal, water may diffuse out of the distal tubules until the urine becomes isotonic. However, the urine entering the collecting ducts of the diseased kidney will be greater in volume and will have a higher sodium concentration. This is due to the fact that none of the mannitol and its osmotically obligated water would be reabsorbed in either kidney. Thus removal of sodium (and an isosmotic amount of water) decreases the concentration of sodium in the remaining urine due to the diluting effect of the water held by mannitol. If the volume of filtrate is greater in the nephrons of the diseased kidney and sodium reabsorption is essentially equal bilaterally, more sodium will be left in the tubules of the diseased kidney per unit volume of residual urine. The removal of water in the collecting ducts (which occurs as a consequence of the prior reabsorption of sodium in the loops of Henle), although essentially equal bilaterally, would result in a smaller increment in osmolality of the urine in the diseased kidney (because of the larger volume presented) than in the normal organ. Hence the diseased kidney would excrete more of its filtered solute and more of its filtered sodium than the normal kidney, and the final urine of the diseased kidney would have a higher sodium concentration and a lower osmolality.

glomerular filtration rate of the *diseased kidney only* was decreased moderately by partially constricting its renal artery. In association with the slight unilateral fall in GFR all of the differences between the two kidneys diminished. The fractions of filtered solute and sodium excreted by the diseased kidney both tended to approximate values of the normal kidney. Moreover, the urinary sodium concentrations of the diseased kidney *decreased* and the urinary osmolalities *increased* so as to approach the concurrent values of the normal kidney. It would thus appear that the slight differences between the diseased kidney and the normal kidney were largely abolished by decreasing the filtration rate of the diseased organ. It may be suggested from these observations that the diseased kidney in a non-uremic environment may sustain some increase in GFR per nephron. Presumably this adaptive change would occur to a much greater degree in the remaining nephrons of the patient with bilateral renal disease and uremia.

On the basis of existing evidence it may be postulated that the ability of the diseased kidney to maintain solute balance is facilitated by two phenomena acting either alone or, more likely, in concert. The first is a continuing osmotic diuresis that results from the high filtered loads of urea in advanced chronic Bright's disease. The second is the development of an increased glomerular filtration rate per functioning nephron. The latter may modify the normal glomerular-tubular balance in such manner as to present more salt and water to the nephrons than the reabsorptive mechanisms can handle.

The possibility that other adaptive changes also occur in the patient with chronic Bright's disease seems likely. The studies on dogs with unilateral renal disease tend to exclude extensive damage to the functioning nephrons of the chronically diseased kidney by the underlying pathologic processes. Yet the patient with bilateral renal disease has certain functional patterns which differ from those of the experimental animal with unilateral renal disease. These differences may relate to the greater decrease in total nephron population and the attendant environmental abnormalities, rather than to selective anatomic damage to functioning nephrons. The increased rate of potassium excretion per residual nephron may be due in part to an associated increase in mineralocorticoid production. The postulated increased rate of hydrogen ion secretion per nephron may be mediated by the development of systemic acidosis. The tendency to hyperphosphatemia may stimulate secondary hyperparathyroidism, which in turn would decrease tubular reabsorption of phosphate and allow normal phosphate excretion by a decreasing nephron mass. The postulated increase in GFR per nephron may be responsible for the relative inability of the patient to excrete a sodium-free urine. When sodium intake is less than optimal the tendency to sodium depletion may lead to secondary aldosteronism, and perhaps the latter contributes to the potassium-losing state occasionally seen in patients with chronic Bright's disease [*56*]. In far advanced renal disease the rate of solute excretion per nephron becomes so great that despite maximal ADH stimulation, the urine entering the collecting ducts may theoretically be hypotonic. This could contribute to permanent isosthenuria (or hyposthenuria) despite the continuing abstraction of solute-free water by the concentrating mechanism. Finally, there is the possibility that certain of the retained metabolites in the uremic patient may have an inhibitory effect on one or more tubular transport mechanisms; this must await future investigation.

RECONSTRUCTION OF SERIAL EVENTS IN THE PATHOLOGIC PHYSIOLOGY OF CHRONIC BRIGHT'S DISEASE

Within the framework of the foregoing concepts an attempt may be made to reconstruct the sequence of events in the patient with progressing chronic Bright's disease. The cardinal event underlying these changes is the destruction of nephrons.

The Initial Phase of Nephron Destruction. As the population of functioning nephrons decreases from normal to 50 per cent of normal, virtually no significant chemical or physiologic abnormalities occur. Sodium, chloride, potassium, phosphate and pH levels all remain normal. Urea and creatinine concentrations rise, but only slightly, since a 50 per cent reduction in GFR effects only an approximate two-fold increase in plasma values, if protein intake, cellular catabolism and total body water remain relatively constant. Hence, with a decrease in GFR from 120 to 60 ml./minute, a blood urea nitrogen of 6 mg. per cent increases to only approximately 12, and a creatinine of 0.8 mg. per cent increases to approximately 1.6.

Although symptoms and signs may appear during the early phases of chronic Bright's disease, these are related not to the direct effects of a decreasing nephron population but rather to the stigmata of the underlying disease (e.g., dysuria in pyelonephritis, arthralgias and fever in systemic lupus erythematosus, etc.). From the point of view of renal function, the patient who has lost half of his nephrons as a consequence of slowly progressing renal disease may sustain no more disability than the subject who is left with one normal kidney following unilateral nephrectomy. This analogy may be extended further, for it is conceivable that the remaining nephrons in the diseased kidney may undergo some degree of compensatory hypertrophy, characterized principally by an increasing rate of glomerular filtration per nephron.

The Intermediate Phase of Nephron Destruction. As the nephron population falls below 50 per cent of normal, more marked chemical changes appear. Urea and creatinine levels continue to increase and definitely exceed the upper limit of the accepted range of normal. In addition, the remaining nephrons may fail to secrete sufficient hydrogen ion to maintain arterial pH levels within the normal range, and a modest systemic acidosis may develop. Owing to the latitude of intact nephrons to increase and decrease sodium excretion, sodium balance may generally be maintained on an unrestricted salt intake. Water balance also is maintained, due to the continuing activity of the concentrating and diluting mechanisms. However, the range over which the urine tonicity may be altered will diminish as the nephron population decreases, and an increasing fraction of water in the urine will be osmotically obligated. For this reason the volume of urine excreted at night approaches that excreted during the day despite the fact that there may be no nocturnal water ingestion.* Nocturia may, therefore, become manifest.

Phosphate balance is ordinarily maintained during the period of intermediate nephron destruction because the reabsorption of phosphate diminishes as filtration rate diminishes. Moreover, as long as normal phosphate concentrations prevail, calcium levels remain normal.

Owing to the capacity of functioning nephrons to increase potassium secretion, potassium balance and normal plasma potassium concentrations are also maintained.

Although there may be few symptoms and signs aside from nocturia, in some patients (but by no means all) anorexia, slight weight loss and an insidious decrease in vigor may occur. Anemia may also make its appearance at this time.*

The Emergence of Renal Failure. As the nephron population falls below 25 to 30 per cent of normal the characteristic abnormalities of the uremic syndrome gradually evolve. Plasma levels of urea and creatinine become markedly elevated and phosphate retention occurs. As phosphate levels rise, calcium levels fall and, characteristically, the greater degree of hyperphosphatemia the more severe the hypocalcemia. Fortunately, until hypocalcemia becomes extreme, the concurrent systemic acidosis decreases the likelihood of tetanic manifestations.

Among the inordinate demands upon the residual nephrons, the need to maintain sodium balance is pre-eminent. As long as dietary intake of sodium varies only moderately from day to day and is neither excessively great nor markedly reduced, balance is maintained. The ability to *vary* excretion in response to changing intake reflects the continuing responsiveness of tubular reabsorption (and GFR) to extrarenal stimuli. The ability of each nephron to excrete a greater than normal fraction of filtered sodium may well be facilitated by the increment in the filtered load of urea and by the development of an increased GFR per nephron. However, both the osmotic diuresis due to urea and the glomerular-tubular imbalance due to the increased GFR per nephron diminish the ability of the kidneys to elaborate a sodium-free urine, and the obligatory salt excretion may exceed 1 or 2 gm. per day.

The excretion of an increased percentage of the filtered salt and water also tends to augment urea excretion. Because the concentration gradient for urea in the tubular urine (and the attendant back-diffusion) results from the reabsorption of water, reabsorption of a decreased fraction of filtered water leads to excretion of proportionately more of the filtered urea. Consequently the rate of urea accumulation may

* As renal disease progresses, the normal diurnal rhythm may reverse and the rate of urine flow may actually be greater during the night than during the day.

* The mechanism of anemia in progressive renal disease still remains in doubt. A presentation of current information as well as an appropriate bibliography are contained in a recent paper by Loge, Lange and Moore [57].

diminish somewhat. The excretion of a large fraction of filtered salt and water has one additional effect. The greater the fraction of filtrate excreted, the more nearly the composition of the final urine approaches that of the parent glomerular filtrate. This is especially noticeable for the concentrating and diluting processes and, despite the evidence already cited that these mechanisms may continue to operate in the residual nephrons, the tonicity of the final urine tends to approach that of the glomerular filtrate.

Potassium excretion by the residual nephrons may increase enough to prevent hyperkalemia on a normal potassium intake. In addition, when systemic acidosis becomes more marked the remaining tubules may increase their rate of hydrogen ion secretion (and bicarbonate ion reconstitution) to maintain balance and thereby prevent the further progression of acidosis so long as there is no increase in the rate of hydrogen ion acquisition from metabolic or exogenous sources.

The Terminal Phase of Chronic Bright's Disease. As the nephron population diminishes further the disabling and widespread derangements of the uremic syndrome become increasingly apparent. Retention of urea, creatinine and phosphate becomes more pronounced. Many additional substances, including sulfate [*58*], magnesium [*59*], urate [*48*], phenols [*60*] and guanidines [*61*], also accumulate in body fluids. For reasons not completely understood, anorexia, nausea and vomiting may become severe, and weight loss, muscle wasting and cachexia may complicate the clinical picture. Because of the obligatory renal loss of salt and water, extrarenal fluid losses (or failure of adequate intake) result in contraction of the extracellular fluid volume, and a functional decrease in GFR may occur. Although the latter response diminishes the rate of osmotic diuresis (due both to a decrease in GFR per nephron and to an attendant fall in the filtered load of urea), thus lessening the further loss of salt and water, it also results in an accelerated rate of accumulation of all substances excreted by filtration. An exacerbation of symptoms and signs is the usual accompaniment of this sequence of events.

Bone marrow suppression, in some instances decreased red cell survival, and occasionally blood loss (principally from the gastrointestional tract) contribute to the progression of anemia, and the anemia in turn may contribute to the development of a high cardiac output.* The latter increases the burden of the myocardium and may lead to congestive heart failure. If hypertension emerges, the cardiovascular load and the likelihood of heart failure are further increased. With the development of congestive failure, cardiac output diminishes (particularly if hypertension is dominant), and the problems of providing adequate oxygenation to the periphery with a decreased oxygen-carrying capacity of the blood, imposed by the anemia, are compounded.

Eventually the nephron population decreases below a critical level and, despite maximal compensation by the surviving units, life may no longer be sustained. In the final days of life urine volume diminishes, and hyperkalemia, progressive acidosis, pericarditis, a diffuse hemorrhagic diathesis, muscular twitching, refractory congestive heart failure, central nervous system derangements, convulsions and coma all may appear. The ultimate result is death.

SUMMARY

Clinical and experimental data relating to the functional capacity of the surviving nephrons of the chronically diseased kidney for the most part support the thesis that these nephrons retain their essential functional integrity regardless of the nature of the underlying form of chronic Bright's disease. There are instances in which specific alterations of function correlate with pathologic involvement of a particular site of the nephron but these appear to represent the exceptions, and in general the more advanced the disease becomes, the less evident are the differentiating features.

Studies on dogs with unilateral renal disease indicate that the functional capacity of the nephrons of the diseased kidney parallels that of the nephrons of the contralateral normal kidney. These data tend to exclude widespread *intrinsic* damage to the functioning nephrons by the underlying pathologic processes. From these observations, as well as from certain supporting clinical and experimental observations, it is suggested that the majority of surviving nephrons in the patient with bilateral renal disease similarly are functionally intact. Concepts of the pathologic physiology of the kidney, based on the "intact nephron hypothesis," are presented.

* The metabolic acidosis may also be a factor in the development of a high cardiac output syndrome.

Within the framework of this hypothesis it is concluded that (1) the diseased kidney consists of a diminished number of nephrons, most of which retain essentially normal functional abilities; (2) certain of the apparent abnormalities in function in bilateral renal disease may relate to adaptive changes imposed by the decreased nephron population and the attendant derangements in body fluids rather than to structural distortion of nephrons; (3) the over-all flexibility of the diseased kidney decreases as the number of constituent nephrons decreases; but (4) there is an orderly and predictable pattern of excretion for all substances.

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Seminar on Mycotic Infections

Actinomycosis and Nocardiosis

A Review of Basic Differences in Therapy

JOSEPH W. PEABODY, JR., M.D. *and* JOHN H. SEABURY, M.D.
Washington, D. C. *New Orleans, Louisiana*

ACTINOMYCOSIS and nocardiosis possess a number of striking similarities, including a close and often indistinguishable clinical resemblance and a close morphologic relationship between the etiologic organisms [*1*]. Essential cultural differences do exist, it is true, but certainly insofar as the tissue reaction is concerned, there may be nothing to distinguish one disease from the other. Let there be no mistake on this score, however; these are two separate and distinct diseases. Nowhere is this more important than in the matter of therapy.

ACTINOMYCOSIS

Actinomycosis is a chronic mycotic infection, more suppurative than granulomatous, with a marked proclivity for forming abscesses and sinus tracts. These extend by contiguity without respect for tissue planes and classically give rise to multiple cutaneous fistulas. Interspersed between these zones of suppuration is a remarkable degree of fibrosis which has the paradoxical effect of walling off the infection while adding a considerable barrier to effective chemotherapy. Dating back to Cope's classic monograph in 1938 [*2*], the clinical spectrum of this disease has been arbitrarily divided into three categories: (1) cervicofacial actinomycosis, (2) thoracic actinomycosis, and (3) abdominal actinomycosis. Cervicofacial infection is not only the most common but is also the most favorable form of the disease, a certain number of such cases having apparently undergone spontaneous remission. The outlook is decidedly worse in instances of thoracic and abdominal actinomycosis, hence it is in these cases that the efficacy of any kind of treatment is best evaluated.

The etiologic organism is an anaerobic or microaerophilic, gram-positive actinomycete, Actinomyces bovis. Due in part to the distinctive tendency of actinomyces to appear in dense clusters (actinomycotic granules) in infected tissues and to coalesce into visible yellowish brown particles (sulfur granules) in pus, actinomycosis was the first of the deep mycoses to be identified in man (1878) [*3*]. Over and above its diagnostic value the formation of the actinomycotic granule also has some bearing on treatment, for a whole colony of actinomyces is apt to exhibit greater *in vitro* resistance to a particular chemotherapeutic agent than does a suspension of the organism [*4*]. If the patient is to be permanently cured, drug therapy must be intense enough to suppress all organisms including those harbored within the protective confines of actinomycotic granules. Failure to penetrate these densely clumped colonies has undoubtedly accounted for many instances of recurrent infection.

Judging from the world-wide distribution of reported cases, actinomycosis is certainly the most ubiquitous of the systemic mycoses. Until recently it was regarded as the most common, a view altered by a better appreciation of the prevalence, in this country at least, of histoplasmosis and coccidioidomycosis. Unlike most other fungus infections actinomycosis is thought to arise from endogenous sources such as infected tonsils, gums and carious teeth, from all of which the etiologic organism, A. bovis, has been recovered. Because of its propensity for saprophytic growth in the oral cavity, pharynx and tracheobronchial tree, even the repeated finding of A. bovis in the sputum is insufficient evidence to prove that radiographically visible pulmonary disease is necessarily due to this fungus. Some of the incredible therapeutic results claimed for outmoded drugs were undoubtedly the result of such misdiagnoses.

Contrary to common belief, A. bovis has

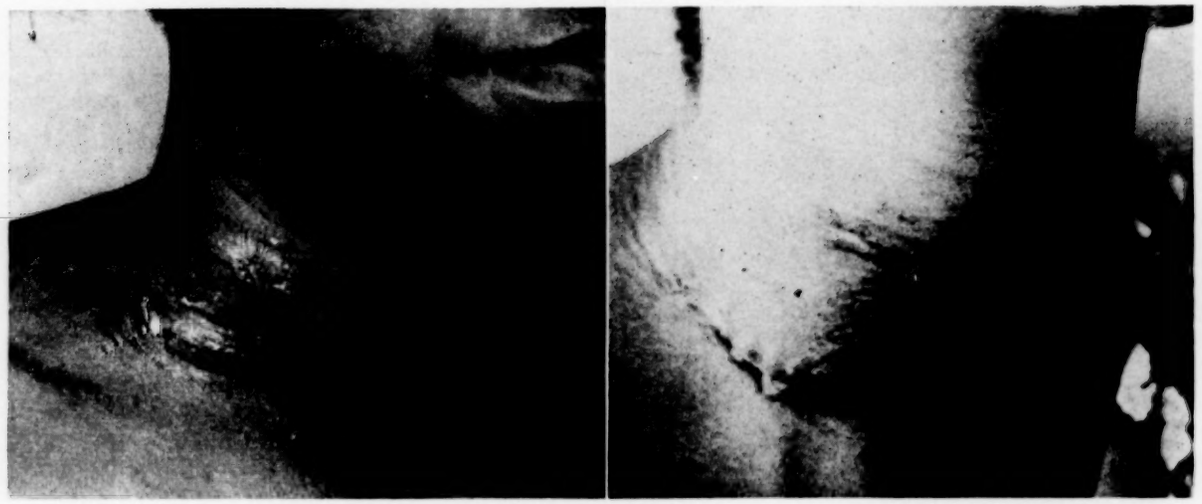


FIG. 1. This fifteen year old Negro girl had cervicofacial actinomycosis of three months' duration. A granuloma pyogenicum occupied the central portion of a lower right molar and contained a central fistulous tract. Numerous fistulous tracts are seen in an area of woody induration (*left*). Treatment with 2.4 million units of procaine penicillin daily for forty-two days resulted in complete healing and normally soft cervical tissues (*right*). The lowermost scar is the result of biopsy. The involved teeth were extracted during treatment.

never been cultured from any source in nature. Completely discredited, therefore, is the age-old view that actinomycosis often results from chewing straw or grain. This is pure fiction, yet it is surprising how many physicians still adhere to this antiquated view. Actually the somewhat higher incidence among farmers is attributable in all probability to their poorer than average dental hygiene. Just why an organism exhibiting as little animal pathogenicity as A. bovis should be capable of attaining such virulence for man is difficult to comprehend. More than likely the actinomyces are mere opportunists which, as a result of trauma (tooth extraction, fractured mandible, etc.) or in conjunction with some bacterial invader, gain access to the tissues where they can assume the role of a pathogen and produce local or even widespread progressive disease.

Granted that a few other systemic mycoses are many times more common, this hardly justifies the current de-emphasis of the importance of actinomycosis. Doubtless many cases of actinomycosis go unrecognized. Take, for example, the matter of anaerobic cultures, which are rarely requested nowadays. A. bovis is by definition an anaerobic or microaerophilic organism with the unique distinction of being the only fungus causing systemic infection that does not grow aerobically at room temperature on ordinary laboratory media. Unfortunately, by the time the need for special cultural technics is appreciated, if indeed it is considered at all, the rather ready susceptibility of A. bovis to most available antibiotics has so suppressed its growth that cultures, even when properly sown, are likely to be negative. Also, any tissue subsequently examined may no longer retain that crucial clue to diagnosis, the actinomycotic granule. Finally, the common practice of giving antibiotics at the first sign of infection regardless of whether it be dental, respiratory, etc. probably accounts for a further apparent decrease in the incidence of the disease. One cannot help but wonder whether actinomycosis is not just as common as ever, but is now arrested so early in its clinical course that the true etiology of some infections is never suspected. Considering only proved cases, however, it has to be listed as a relatively uncommon disease.

The therapy of established actinomycotic infections is a complicated problem much akin in general principle to the management of tuberculosis. This is not surprising when one considers that the mycobacteria, actinomyces and nocardia are all members of the order actinomycetales and are presumably more closely related to one another than to ordinary bacteria or more complex fungi. All three are chronic granulomatous diseases requiring intensive long term treatment, overtreatment in fact, if relapse is to be prevented. The application of sound surgical principles of drainage and excision is as essential in one disease as in the

others. Recent years have witnessed a dramatic change in the outlook for all three diseases, the discouraging results of the preantibiotic era having been converted in most instances to frank optimism by the introduction of effective chemotherapy.

In earlier years therapeutic efficacy in treating actinomycosis had been ascribed to a number of agents, chief among them being iodides, thymol, copper sulfate and autogenous vaccines. That any of these are really effective is open to serious question. Yet in the case of thymol there were quite a few reports attesting its value [*5–10*]. In one instance an extensive lesion in the upper lobe of the right lung associated with sulfur granules in the sputum cleared with remarkable ease after just seventeen days of thymol administration [*9*]. In another patient a course of thymol arrested a cervicofacial infection that had previously failed to respond to almost a month of intensive sulfonamide therapy [*10*]. Even so, since the advent of more effective drugs, its use, like that of the other drugs mentioned, has largely been abandoned.

Somehow the idea persists that iodides are invaluable, although there is no sound basis for this view. Years ago the initial utilization of iodides for human actinomycosis was the result of mistaken identity, actinomycosis and its animal analogue, lumpy jaw of cattle, having been confused with woody tongue or actinobacillosis of cattle and pigs. The latter disease, as the term implies, is caused not by a fungus but by an actinobacillus that is specifically responsive to iodides whereas actinomyces are not. Several workers [*11,12*] found luxuriant growth of actinomyces in media containing 2 per cent potassium iodide, a point recently confirmed by the *in vitro* studies of Suter and Vaughan [*13*].

X-ray therapy once enjoyed wide usage and is still advocated occasionally in cervicofacial infections, despite the fact that there would seem to be little justification for its continued use. Perhaps the best commentary on its relative value is that found in the report by Stewart-Harrison (1934) [*14*] who claimed good results in twenty cervicofacial infections but no benefit in eight cases of pulmonary or abdominal actinomycosis, all of which ultimately proved fatal.

Of the many time-honored forms of treatment surgery is the only one that has not become obsolete. Waring (1905) [*15*] was the first to stress its importance and this has been subsequently re-emphasized by innumerable surgeons [*16–23*]. The role of surgery is concerned primarily with the drainage of abscesses and empyemas, but because of the extensive fibrosis peculiar to actinomycotic infections radical surgical excision is sometimes necessary. In fact, so impressed were the Johns Hopkins group by the difficulty in getting therapeutic doses of penicillin into these dense avascular areas that lately they have routinely employed wide surgical excision of infected tissues in conjunction with massive penicillin administration [*25*]. By this bold combined approach their results improved appreciably, reaching an 88 per cent cure rate.

The similarity alluded to between actinomycosis and tuberculosis also applies to the question of surgical therapy for pulmonary disease. In actinomycosis, as in tuberculosis, pulmonary resection has a definite place in removing a residual focus, persistent cavity or otherwise destroyed portion of lung. One of the first to apply this principle was Kay [*23,24*] whose most important contribution was to emphasize the hazards of too limited a resection. To preclude the possibility of postoperative spread, reactivation or empyema the use of chemotherapeutic coverage is essential and should be maintained for prolonged periods, certainly for no less than two to three months.

Surgical resection is apt to be applied unwittingly in some cases of pulmonary actinomycosis through the erroneous impression that one is dealing with a bronchial carcinoma. Both radiographically and on gross examination an actinomycotic abscess of the lung can closely resemble a tumor mass. Bates and Cruickshank [*26*] in a recent study of eighty-five cases of thoracic actinomycosis included seven patients treated by pulmonary resection, none of whom was operated upon with the correct preoperative diagnosis. This experience has been duplicated by others [*27–30*] and attention has been directed to the little appreciated tendency for pulmonary actinomycosis to produce a dense hilar lesion extending out into lung parenchyma like a bulky bronchial neoplasm [*30*].

The first dramatic change in the treatment of actinomycosis occurred in 1938, when the sulfonamides became available. Within a few years there appeared ample evidence of their value [*31–40*]. Several of these cases were extremely severe, so much so that their recovery was regarded as miraculous. The patient of Miller and Fell [*34*] is a good case in point. An

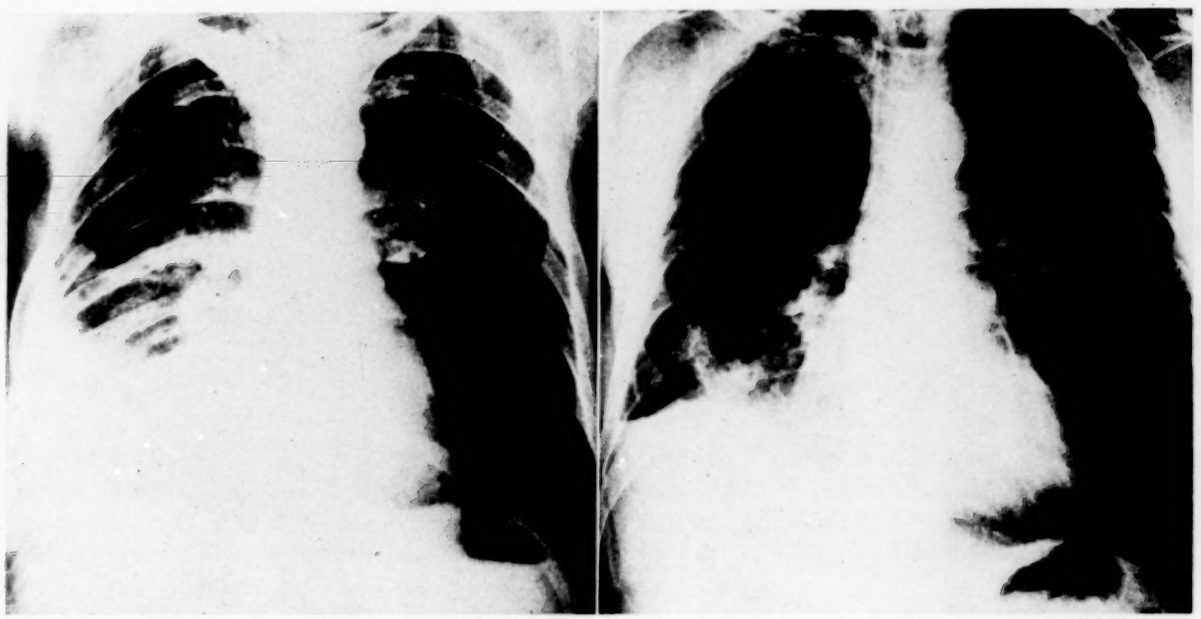


FIG. 2. Middle-aged white man with multiple draining sinuses over the anterior chest. A. bovis had been recovered from purulent drainage, but previous intermittent treatment with penicillin and sulfadiazine had been inadequate. Chest roentgenogram (*left*) revealed a right empyema. Six months after the institution of intensive penicillin therapy all sinuses had healed and there was extensive clearing on chest roentgenogram (*right*).

eleven year old boy ill with abdominal actinomycosis was growing worse when sulfanilamide therapy was begun in January 1938. Thymol, x-ray therapy and iodides had all been tried without any alteration of his downhill course. Soon after the institution of sulfonamide therapy (2 gm. per day), the patient improved strikingly but the drug was continued for a total of ten months before he was considered cured. The necessity for long term therapy is nicely illustrated by this patient treated at a time when more attention was being paid to the danger of the drug than to the hazard of the disease.

In 1941 Dobson, Holman and Cutting [*41*] published the first of two papers on the chemotherapy of actinomycosis, re-emphasizing the importance of sulfanilamide for relatively long periods and citing three arrested cases, two of them quite severe. Cutting and Gebhardt [*42*] claimed that sulfadiazine and sulfathiazole deserved continued trial on the basis of *in vitro* sensitivity studies, but it is probable that the organism with which they were working was not A. bovis. Later Keeney, Ajello and Lankford [*43*] in evaluating the sulfonamides found their inhibitory effect to be considerably less than spectacular. Finding themselves unable to confirm the work of Cutting and Gebhardt [*42*], they injected a word of caution as to the expectancy of cure with the sulfonamides. Abraham and Miller [*44*] concluded from their *in vitro* investigations of two strains of A. bovis that the sensitivity to sulfathiazole and sulfadiazine was insufficient to justify their clinical use. Nevertheless, sulfadiazine temporarily remained the drug of choice until penicillin ultimately established its superiority.

The potential value of penicillin in actinomycosis was first cited in 1941 by the Oxford investigators [*45*] who found a strain of A. bovis that was no different in its *in vitro* susceptibility to penicillin than were many of the more sensitive bacteria. Almost two years passed before Fisher [*46*] mentioned two additional strains being quite sensitive to penicillin. After finding the organism inhibited and apparently killed by a concentration of 0.01 units of penicillin per ml. of medium, Keeney, Ajello and Lankford [*47*] commented that A. bovis in its susceptibility to penicillin actually resembled a bacterium more than a fungus.

Nevertheless the first references to its clinical utilization were not very encouraging. Florey and Florey [*48*] used penicillin in several cases in which the diagnosis seems poorly documented. One patient, for example, had actinomyces repeatedly demonstrated in the sputum, although most of his complaints were referable to

the abdomen. Penicillin provided no apparent benefit, but this is readily understandable considering the dosage (10,000 to 20,000 units every four hours), route of administration (via duodenal tube) and duration of treatment (six days). The report by Keefer et al. [*49*] was likewise inauspicious, only one of three patients with actinomycosis treated with penicillin escaping a fatal outcome. However, there were no details given as to the extent of disease and amount of therapy. Lyons, on the other hand, in summarizing the United States Army experience with penicillin [*50*], made reference to four patients with actinomycosis, all of whom improved on penicillin. Again no details were provided other than to say that follow-up was too brief to be conclusive. The first real note of enthusiasm was sounded by Herrell in 1944 [*51*]. Of three patients with cervicofacial actinomycosis treated with penicillin, two recovered. One case was considered a therapeutic failure. A fourth patient with abdominal actinomycosis and carcinoma of the colon also had an unsatisfactory response, as might be expected.

Ample clinical confirmation soon followed. Walker and Hamilton [*52*] in a report of six cases included one patient with a widely disseminated infection who responded dramatically to penicillin after an initial failure to improve on sulfonamides. A similar experience was reported [*53*] in a patient with infected war wounds in whom subcutaneous abscesses and pleural effusion, presumably actinomycotic in origin, developed. There was no response to sulfonamides but the disease was arrested by two courses of penicillin. To illustrate why penicillin failures might occur, attention should be directed to the latter authors' concern over a twenty-eight day period of penicillin administration which they considered "very long" and the daily dose of 200,000 units which they regarded as "unusually high." As a consequence, instances of inadequate therapy were bound to occur, sometimes with tragic results. Shulman [*54*], for example, referred to a patient who in the year prior to death from actinomycosis had received five separate courses of penicillin, none of them for a very long period yet each followed by temporary improvement. Although as yet unconvinced of the relative superiority of penicillin over sulfadiazine, Dobson and Cutting [*55*] were well aware of the need for prolonged treatment. Several of their patients received either sulfadiazine or penicillin for periods close to one year before being considered cured.

Perhaps the deciding vote in favor of penicillin therapy was contained in the report of Nichols and Herrell published in summary form in 1947 [*56*] and in greater detail the following year [*57*]. Included were the results of treatment of forty-six patients with actinomycosis receiving what was considered adequate therapy as opposed to a comparable number who had not. For cervicofacial infections recovery was approximately the same in both groups (over 90 per cent), thus emphasizing the relatively good prognosis for this form of the disease. Worth noting, however, was the much shorter period of disability and the much quicker healing of sinuses among those receiving penicillin. A satisfactory result followed an average of two months of penicillin therapy as compared with an average of six months treatment by other means.

In the pulmonary and abdominal cases the difference was even more striking. Whereas only one of thirteen pulmonary infections improved without penicillin, there were five recoveries among nine patients with pulmonary actinomycosis treated with penicillin, a recovery rate of 55 per cent. Among those with abdominal infections there was only one purported recovery of fourteen patients receiving no penicillin in contrast to eight cured patients of ten treated with penicillin, an 80 per cent recovery rate. All strains of A. bovis cultured from these patients were sensitive to penicillin *in vitro*, being inhibited by 0.01 to 0.1 units of penicillin per ml. of culture medium. The authors recommended administration of at least 500,000 units daily, intramuscularly or intravenously, for a minimum of six weeks.

Over the succeeding years it has become obvious that higher doses of penicillin would be required, especially in disseminated infections and in severe types of pulmonary and abdominal actinomycosis. The need for massive penicillin therapy is well exemplified in the report by Sanford and Barnes [*58*]. Two patients with abdominal actinomycosis had regressed after prolonged penicillin and sulfadiazine administration. One had received 128 million units of penicillin and 874 gm. of the sulfonamides over the preceding eight months; the other, over 58 million units of penicillin and 1,000 gm. of the sulfonamides during the previous nine months. Striking improvement followed the institution of massive doses of penicillin. The first patient

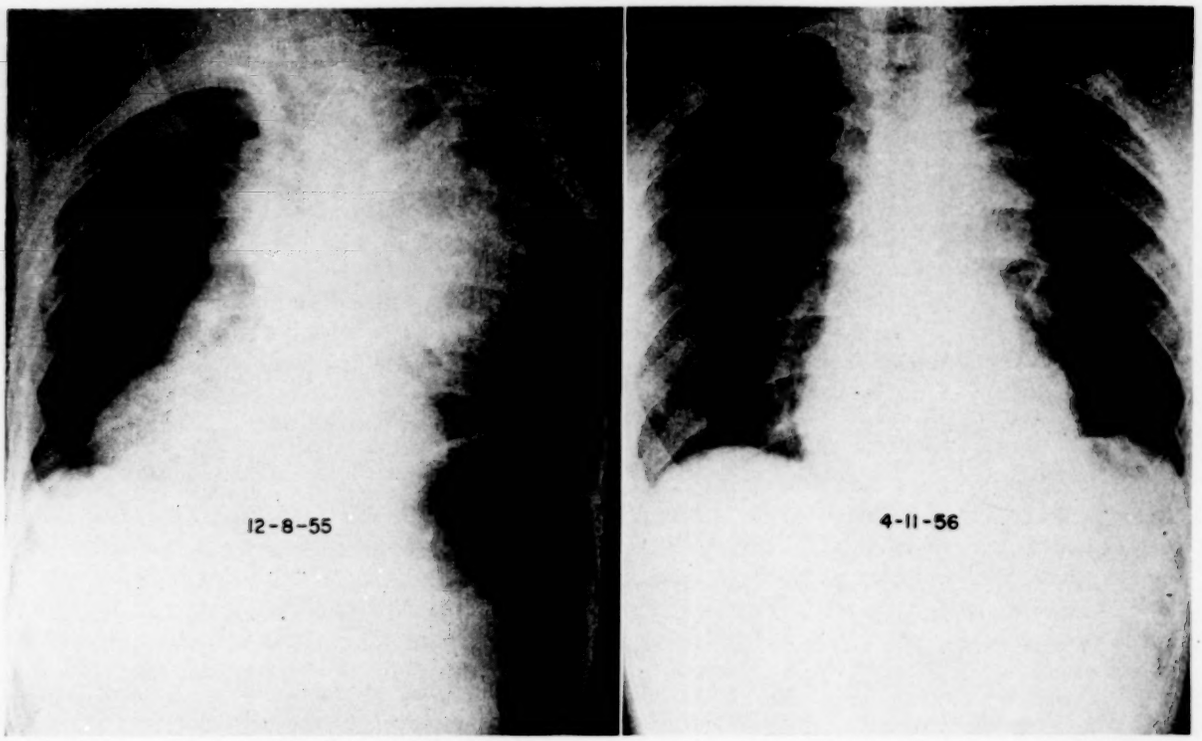


FIG. 3. Young Negro man with severe back pain of one year's duration recently accompanied by fever. Chest roentgenograms disclosed a homogeneous infiltration in the left upper lung field with marked mediastinal widening most marked inferiorly (*left*). Roentgenograms of the spine showed involvement of the mid-thoracic vertebrae. The mediastinal abscess pointed posteriorly. Surgical drainage produced considerable pus from which A. bovis was cultured. On vigorous prolonged penicillin therapy, augmented for several months with sulfadiazine and body cast, healing gradually ensued (*right*). From: Peabody, J. W., Jr. and Seabury, J. H. Actinomycosis and nocardiosis. *J. Chron. Dis.*, 5: 374, 1957.

received more than 644 million units of penicillin over the next sixty-seven days; the second, over 586 million units during the following forty-eight days. Both patients recovered without further incident.

For the average case of actinomycosis, penicillin remains the drug of choice. It must be given in moderately high dosage and for sustained periods of time. We routinely use 1 to 6 million units of penicillin daily for a minimum of six to eight weeks. For severe cases 12 million units per day is not excessive. In fact, Harvey and co-workers [*25*] have adopted the standard practice of giving a daily intravenous dose of 10 to 20 million units of penicillin. Certainly in severe cases this may be advisable. Just as in tuberculosis, treatment must be prolonged for many months and sometimes for as much as a year or more, not only to eradicate all signs of activity of the disease but to preclude the possibility of reactivation.

Despite its general effectiveness the continued use of penicillin was associated with its share of treatment failures, which in most instances could be traced to dosages that by current standards would be considered inadequate. Invariably there arose the question of resistant organisms. In 1944 Christie and Garrod [*59*] tried to correlate the relative penicillin sensitivity of four strains of A. bovis to the response to therapy. Two organisms were very sensitive to penicillin and penicillin therapy was quite successful in both instances. The other two strains were as much as eight times more resistant to penicillin; both of these cases were said to be unamenable to therapy. Several other investigators likewise found different strains to vary significantly in their *in vitro* susceptibility to penicillin [*55,60*].

On the other hand, Nichols and Herrell [*57*], after testing every strain of A. bovis recovered from clinical material at the Mayo Clinic, claimed that all strains were penicillin-sensitive, being inhibited by 0.01 to 0.1 units of penicillin per ml. of culture medium. Boand and Novak [*61*] examined six strains and showed all six to

be sensitive to 0.05 to 0.5 units of penicillin per ml. of culture medium. Furthermore, only a minimal degree of resistance with successive serial transfers developed in the organisms. This was in sharp contrast to streptomycin to which they showed a 250-fold increase in resistance after ten transfers. Garrod [*62*] was able to show that A. bovis is fairly constant in its sensitivity to penicillin. Of thirty strains studied, none required more than 0.25 units of penicillin per ml. of culture medium to inhibit growth and the vast majority required less.

Holm [*4*] has reported some extremely interesting investigational data that serves to clarify the apparent discrepancy between sensitivity studies in different laboratories. Testing suspensions of twenty-nine indisputably human pathogenic anaerobic actinomyces, he found each to be just as sensitive as staphylococci to penicillin. However when he tested the penicillin sensitivity of whole colonies, the various strains fell in their responsiveness into two distinct groups, one being much more resistant than Staphylococcus aureus, the other being only slightly more resistant. He attributed this to the compactness of the colony which renders it relatively impermeable to any therapeutic agent. His results have been confirmed by Garrod [*62*] who found the concentration of penicillin required to inhibit growth from whole colonies of actinomyces to be five times that necessary to inhibit growth of a ground up suspension. Such an explanation does help resolve some of the conflicting sensitivity studies. More important still, it explains why such high dosage and such sustained administration of penicillin is required, for the actinomyces have the very unique tendency to duplicate their *in vitro* colonial growth in tissue by the formation of granules, and the permanency of cure depends upon how thoroughly all organisms are destroyed, including those lying deep within the granules. Exceptionally high concentrations of penicillin are necessary, therefore, first to penetrate areas of fibrosis, and then to penetrate the colony of the fungus itself [*62*].

At the same time one must be cognizant of the fact that an occasional failure will attend the treatment of systemic actinomycosis with penicillin alone. In an attempt to obviate this possibility it was once popular to give penicillin and sulfadiazine in combination [*63–66*], although the *in vitro* studies of Dobson and Cutting [*55*] indicated that the two drugs together had no synergistic effect and in some instances the combination appeared even less effective than sulfadiazine alone. Nowadays, aided by current emphasis on the broad-spectrum antibiotics, the combined use of penicillin and sulfadiazine is seldom advocated, although Delarue still contends that together they comprise the best available treatment [*67*]. Generally speaking, the broad-spectrum antibiotics do show greater *in vitro* effectiveness against A. bovis than does sulfadiazine. Even so, the prolonged administration of a broad-spectrum antibiotic has certain inherent hazards and for this reason their routine use either alone or in combination is probably an unwise choice. If the patient is sensitized to penicillin or fails to respond to adequate penicillin therapy, this is quite a different matter.

In selecting a substitute for penicillin there are a number of possibilities. Streptomycin is one of the less effective drugs, yet in a few instances it has proved remarkably successful [*68–70*], having on one occasion arrested the disease after penicillin, sulfonamides, iodides and various surgical measures had failed [*70*]. The fact that relatively high serum concentrations of streptomycin are attainable undoubtedly accounts for its occasional success, for Garrod [*71*] in testing twelve strains of A. bovis demonstrated that the minimum inhibitory concentration of streptomycin was almost fifty times that of penicillin and about twelve times that of the more effective broad-spectrum antibiotics. A few strains were considerably more sensitive, but add to their initial sensitivity the tendency to develop quickly as much as 250-fold increase in resistance to streptomycin *in vitro* [*61*], and it becomes an inferior drug for treating the average case of actinomycosis. Dihydrostreptomycin has also been evaluated and found to be among the least encouraging of the available antibiotics [*13*].

Nevertheless, from the theoretical point of view there is another side to this question. Jepson, Rose and Tonkin [*72*], for example, advocate the combination of penicillin and streptomycin for actinomycosis, the streptomycin being intended not for the actinomyces but against the other organisms that are nearly always present. In 1905 Wright [*73*] was impressed with the frequency with which various bacteria accompanied A. bovis, often being intimately associated with granules. Special attention has been paid Actinobacillus actinomycetem comitans, originally recovered from

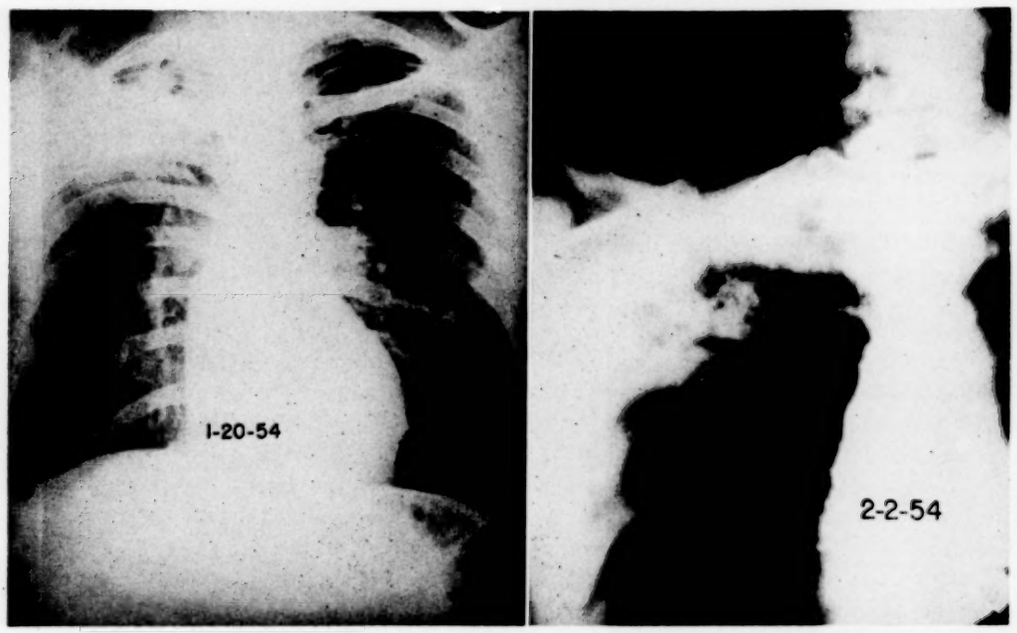


FIG. 4. Thirty-one year old Negro man with cavitary lesion in the right upper lung field (*left*). Sputum was persistently loaded with gram-positive actinomyces and A. bovis was repeatedly recovered in culture. Despite several weeks' intensive antibiotic therapy the cavity was unchanged. Resected specimen showed a bronchiectatic cavity without any evidence of actinomycosis. There is insufficient proof to justify a diagnosis of actinomycosis. Whether the actinomyces were saprophytic or responsible for the lung abscess is a matter of conjecture. Such cases should not be cited as proved instances of actinomycosis.

actinomycotic lesions by Klinger [*74*] and subsequently by others [*74–77*]. Holm [*4,78,79*] is of the opinion that other organisms can invariably be found and refers to them as "other microbes" or "associates." These are sometimes sensitive to penicillin but they are for the most part gram-negative anaerobic bacilli or coccobacilli which tend to be penicillin resistant. It is generally agreed that these organisms are partly responsible for initiating actinomycotic infections, but what their role might be in perpetuating the infection is not known. In any event, when the response to penicillin is poor one might keep in mind the possibility of a resistant bacterial associate, although we ourselves would be more inclined to suspect an undrained abscess or some more significant underlying disease, such as an unrecognized malignant lesion or tuberculosis, that might account for persistence of the infection.

There have been many *in vitro* sensitivity studies indicating that the broad-spectrum antibiotics should be successful in treating actinomycosis. Littman, Phillips and Fusillo [*80*] tested six strains of A. bovis and found them to be inhibited in concentrations of chloramphenicol ranging from 0.005 to 0.1 μg. per ml., indeed a marked degree of sensitivity. Strauss et al. [*60*] evaluated a number of antibiotics and found chloramphenicol to be as effective as penicillin, although none of the three strains tested manifested the extremely high sensitivity reported by Littman and co-workers [*80*]. Garrod's study [*71*] showed that all three of the original broad-spectrum antibiotics should be therapeutically effective, oxytetracycline and chloramphenicol producing greater *in vitro* inhibition than chlortetracycline although by no means as much as penicillin. Moreover, because of the instability of chlortetracycline he thought that any test such as this requiring prolonged incubation provided an unfair assay of the true activity of the drug. Hence, he suspected that it probably approximates the other two in real effectiveness.

Howell [*81*] found oxytetracycline to be bacteriostatic for all strains of actinomyces tested in a concentration of 5 μg. per ml. Fusillo et al. [*82*], working with three strains of A. bovis, demonstrated inhibition of all strains by erythromycin in 0.1 μg. per ml. concentration. Suter and Vaughan [*13*] confirmed the findings of Fusillo [*82*] with regard to the extreme sensitivity to erythromycin, finding marked inhibition of

growth in concentrations of 0.005 μg. per ml. The three strains tested were also highly sensitive to bacitracin and carbomycin, and to a slightly lesser degree to chlortetracycline, tetracycline, oxytetracycline and chloramphenicol. An *in vivo* study in mice by Geister and Meyer [*83*] showed chlortetracycline and penicillin to be of about the same order of effectiveness.

It is not surprising, therefore, that clinical cases of actinomycosis should prove amenable to the broad-spectrum antibiotics. Well substantiated cures have now been reported with chlortetracycline [*84–90*], chloramphenicol [*91*], oxytetracycline [*92*], tetracycline [*93*] and erythromycin [*94*]. Other reports have confirmed their effectiveness in combination with other chemotherapeutic agents or with one another [*95–99*]. In addition there have been several patients cured with administration of isoniazid [*100–102*], in doses a good deal higher than for tuberculosis, and with stilbamidine [*103*].

Regardless of such claims, penicillin remains the undisputed drug of choice. Should supplemental therapy become necessary, *in vitro* sensitivity studies provide the best guide to a successful choice.

NOCARDIOSIS

Nocardiosis, which is comparable to actinomycosis in so many respects, is likewise a chronic suppurative mycotic infection with a similar although less pronounced propensity for abscess and sinus tract formation but a more marked capacity for hematogenous dissemination. The primary site of involvement is usually the lungs. Especially noteworthy is the tendency for it to spread to the brain where it may resemble a brain tumor, brain abscess or meningitis.

Nocardiosis, despite its occurrence in all parts of the world and notwithstanding the ease with which nocardia can be recovered in culture, has been infrequently recognized, usually being misdiagnosed as actinomycosis or tuberculosis. Even when its true identity has been appreciated, it is apt to be regarded as little more than an unusual and often fatal variant of actinomycosis. Being unamenable to indiscriminate chemotherapy, nocardiosis is not likely to be eradicated in the subclinical stage, as is actinomycosis. Hence, while the importance of actinomycosis may be diminishing, that of nocardiosis seems to be growing. We suspect that it is a disease far more common than the number of reported cases would suggest.

Easily the most important member of the genus nocardia is Nocardia asteroides, an aerobic, gram-positive, branching filamentous fungus that is variably acid-fast and is responsible for most cases of nocardiosis. For several reasons its identity may be missed. From their tendency to fragment into short segments, nocardia may pass for bacteria (as may actinomyces). Being acid-fast and often associated with chronic lung disease, N. asteroides may be confused with Mycobacterium tuberculosis. Because of its relatively rapid growth and chromogenicity it may be discarded as a saprophytic mycobacterium. Another source of confusion is the seldom appreciated ability of nocardia to form actinomycotic granules quite like those of actinomycosis. Also, nocardia too can reside in the human body in a purely saprophytic role. The chief difference between the two is the preference of actinomyces for teeth, gums and tonsils, and the predilection of nocardia for the tracheobronchial tree particularly in patients with bronchiectasis or other chronic bronchopulmonary disease. One must be wary, therefore, of attaching too much significance to every cultural recovery of nocardia.

Over and above the fact that one is anaerobic and the other aerobic, actinomyces and nocardia exhibit other important differences. In contrast to the fastidious growth requirements of actinomyces, the nocardia are easily cultured, growing well on all common laboratory media both at room and incubator temperatures. Unlike the actinomyces, nocardia are readily recoverable from sources in nature. N. asteroides is usually highly pathogenic for laboratory animals, whereas the inoculation of the same animals with pure cultures of A. bovis is seldom capable of reproducing the disease. Certainly the most important distinction lies in the varying drug sensitivities and contrasting therapeutic response of the two diseases.

Partly because of greater virulence of the organism and partly because of its greater resistance to drug therapy, nocardiosis represents a more trying therapeutic problem than does actinomycosis and carries with it a lower likelihood of success. All too often the diagnosis is made so late in the course of the disease that therapy is worthless. Also in a regrettably large number of cases the correct diagnosis is established only at autopsy. To regard the disease as incurable is unwarranted, however, for there

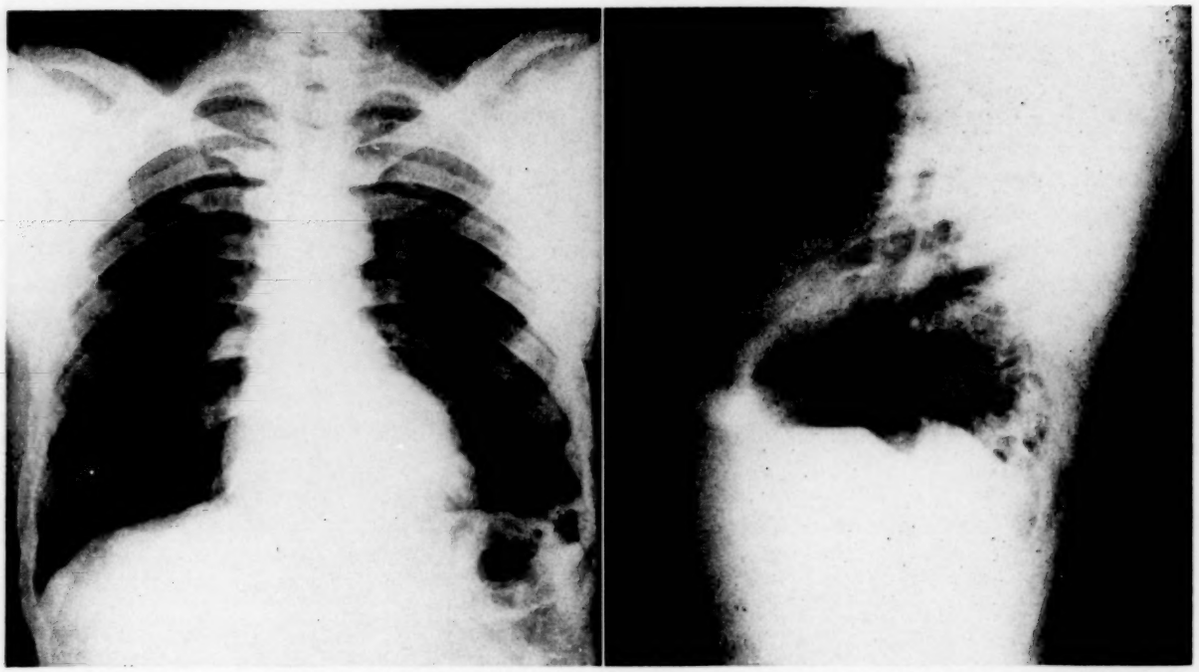


FIG. 5. A young Negro man in whom innumerable draining sinuses developed involving the neck, face, chest, back and abdomen following a tooth extraction four years earlier. Routine chest roentgenograms revealed an osteolytic lesion in the seventh left anterior rib but no evident pulmonary disease. N. asteroides was cultured from the chest and inguinal sinuses as well as from the marrow of the involved rib. Sulfadiazine was given without interruption for the next three and a half years before all sinuses healed. He has remained well.

have been a small but mounting number of arrested cases. Provided the diagnosis is made reasonably early, the institution of vigorous unrelenting chemotherapy provides a fairly good chance for the patient's recovery.

Before sulfonamides became available, the treatment of nocardiosis was no different than that of actinomycosis. Instead of an occasional salvaged case, however, the results were uniformly bad. Seldom was the diagnosis established in time to permit treatment of any kind, and then it was largely supportive. Spontaneous remissions were almost unheard of. Surgical measures alone were ineffectual. So frustrating an experience was it that the senior author (J. H. S.) in several early cases tried rectal ether instillations and repeated periods of deep ether anesthesia after noting in the laboratory how sensitive to ether vapor were colonies of nocardia. Unfortunately there was no significant response to this or any other form of therapy prior to the introduction of the sulfonamides.

Success in treating systemic nocardiosis was not reported until 1944, when Benbow, Smith and Grimson at Duke University published an account of two arrested cases [*104*]. Both received sulfonamides because of their recently established success against actinomycosis. Actually, both patients manifested very indolent disease processes; the first presenting a nocardial pneumonitis associated with draining sinuses in the neck, chest and hip; the second, a subcutaneous abscess on the chest wall followed by multiple lung abscesses and perirectal abscess. The first patient received only a three-week course of sulfanilamide followed by x-ray therapy, local compresses, potassium iodide in large doses, multiple surgical drainages and excisions of sinuses, multiple blood transfusions and general supportive measures. The nocardial pneumonitis cleared and the draining sinuses in the neck, chest and hip disappeared. The other patient received sulfadiazine, presumably for no more than two weeks, together with potassium iodide, transfusions, surgical drainage, vitamins and x-ray therapy. Again there was a surprisingly good therapeutic response. In 1946 Shaw, Holt and Ray [*105*] reported a patient with disseminated nocardosis who was eventually cured by combined penicillin and sulfadiazine administration following drainage of an abscess in the right buttock and empyema in the left pleural space. Potassium iodide and thymol had not been beneficial.

Although the most marked improvement followed the institution of sulfadiazine, recurrence of the empyema developed more than a year later, and on that occasion there was a prompt response to penicillin alone. Thus, in none of these cases was there sufficient grounds to consider the sulfonamides to have been a crucial or even very important part of treatment.

However, better proof soon followed. Kirby and McNaught [*106*] demonstrated the effectiveness of sulfadiazine in a patient with pulmonary nocardiosis who responded repeatedly to short courses of this drug. Due apparently to inadequate therapy, death ultimately resulted from disseminated disease. One could hardly ask for a more forceful example of the need for intensive long term treatment. Glover and co-workers at the Mayo Clinic [*107*] reported another arrested case in 1948. The patient, a physician ill with nocardial pneumonitis and empyema, failed to respond to penicillin and streptomycin. The administration of sulfadiazine, however, 1,268 gm. administered orally over a five-month period and 75 gm. intrapleurally, succeeded in eradicating the disease permanently [*108*]. Also in 1948, a patient with severe nocardial meningitis was reported cured by combined therapy with sulfadiazine and penicillin [*109*]. In addition, a patient with nocardial cervical adenitis secondary to a tooth extraction was apparently cured by extended sulfadiazine administration [*110*]. In 1951 a third successfully treated case was reported from Duke University [*111*], once again illustrating the need for vigorous sulfonamide therapy in conjunction with surgical drainage. The case of Thomas and Pulaski [*112*] is instructive in that improvement ensued, not after tetracycline and erythromycin were administered, but only after sulfadiazine was instituted. The same was true of Webster's cases [*113*]. In four instances sulfadiazine eventually produced complete recovery, whereas in three additional patients chemotherapy, although beneficial, was being continued because of persistence of active disease. Larsen, Diamond and Collins [*114*] have recently presented seven cases of nocardiosis, five of them occurring as a complication of a malignant lesion. Although sensitivity tests were encouraging, antibiotic therapy was not particularly helpful in treating the infections. The authors concluded that sulfonamides might well have proved more effective and should have been used. Reports of at least seven additional cases cured by sulfadiazine have appeared [*1,115–117*], including four cases of our own [*1*].

Insofar as we can determine, only one patient has been cured with administration of the broad-spectrum antibiotics. This was a case of pulmonary nocardiosis reported from Puerto Rico in 1957 [*118*]. Penicillin, tetracycline and small doses of sulfadiazine had been given without any apparent success. Even though the organism was resistant to chloramphenicol *in vitro*, administration of this drug ultimately achieved a good result. Nevertheless, there is ample testimony that sulfadiazine is the drug of choice.

N. asteroides is relatively resistant, however, and for maximum effectiveness it is probably advisable to administer an additional drug along with it for whatever inhibitory effect it may add. Unfortunately, the choice of an ancillary drug is not always a simple matter. Sensitivity studies can be quite deceptive, drugs that seem efficacious *in vitro* often manifesting little clinical benefit. For instance, both Strauss' group [*60*] and Runyon [*119*] have shown that antibiotics like chlortetracycline and streptomycin may exert a greater suppressive action *in vitro* than does sulfadiazine and yet be decidedly inferior to sulfadiazine in clinical effectiveness. The crucial animal protection experiments of Strauss et al. [*60*] have shown sodium sulfadiazine to provide almost perfect protection against N. asteroides. Halde and Newstrand [*120*] found sulfadiazine to be relatively ineffective *in vitro* against most strains of N. asteroides, but the same drug in fairly large dosage significantly lowered the death rate in mice infected with one of the non-sensitive strains. From this they concluded that fungistatic action at concentrations below that required for complete inhibition of growth is all that is needed to enable the host's natural defense mechanisms to overcome the infection.

In our experience fresh isolates of N. asteroides are usually significantly inhibited by sulfadiazine in a concentration of 10 mg. per cent but the degree of inhibition is not augmented by increasing the concentration four- or fivefold. Some strains are similarly suppressed by streptomycin without any additional inhibitory effect from increasing the concentration of streptomycin. We have observed the same phenomenon with broad-spectrum antibiotics. Stilbamidine and 2-hydroxystilbamidine may be nocardiostatic to the point of producing complete

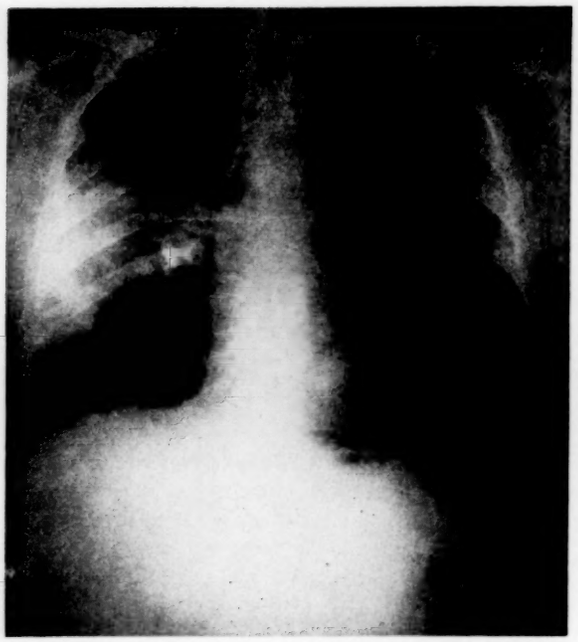


FIG. 6A. A thirty-nine year old electrician with cough and right pleuritic chest pain of about one year's duration. Chest roentgenograms revealed a dense infiltration involving the right midlung field.



FIG. 6B. Same patient. An abscess later appeared on the right shoulder, and N. asteroides was obtained in pure culture from the drainage site. He received nine months' treatment with sulfadiazine and remains well.

inhibition by concentrations attainable in man. MRD-112, a fencholate, also is quite effective, achieving in some instances complete suppression of growth in a concentration of 1 mg. per ml. of medium. Amphotericin B, so promising against many of the more resistant mycoses, has no apparent suppressive effect on nocardia *in vitro*.

In dealing with sixteen cases of nocardiosis we can claim only limited success. However, in the majority of the fatal cases the diagnosis was made at autopsy or at best in the terminal stage. Five patients are considered cured. Another patient with coexisting nocardiosis and tuberculosis was apparently cured following prolonged drug therapy and pneumonectomy for residual disease, but succumbed postoperatively of a pulmonary embolus. In addition, we have had one patient with nocardiosis of the cervical lymph nodes due to Nocardia brasiliensis, which healed during tetracycline therapy.

Our experience leads us to believe that the best chance for recovery rests in vigorous chemotherapy combined, when indicated, with the intelligent use of surgical drainage or resection. The combination of sulfadiazine with one of the more effective broad-spectrum antibiotics or streptomycin is probably a wise choice initially. A daily dose of 4 to 6 gm. of sulfadiazine combined with 2 gm. of the antibiotic of choice is a reasonable regimen for an adult, but the sulfadiazine may be increased to 8 or 9 gm. per day in severely ill patients. After sensitivity tests have been reported, one may choose to modify therapy, particularly when the initial response is disappointing. In this connection it must be remembered that nocardiosis, like tuberculosis, is basically a chronic disease, and immediate amelioration of symptoms or prompt improvement in the roentgenogram is not to be expected.

The question of duration of therapy is like that of tuberculosis and actinomycosis. If recurrence is to be prevented, treatment should certainly be continued for several months after clinical manifestations have disappeared and the disease has stabilized. One of our patients required three years of continuous therapy before all sinus tracts closed and permanent cure was effected.

Surgery may be necessary to remove nocardial residua and is of course indispensable for the evacuation of abscesses and empyemas. Histologically there tends to be less fibrosis associated with nocardiosis than with actinomycosis; hence the reason for high persistent dosage lies more in the organism's virulence and refractoriness to chemotherapy than to any difficulty in getting adequate concentrations because of scarring. Perhaps this also accounts for the



FIG. 7A. A fifty-six year old white man with pain in the left side of the chest of several months' duration, mild temperature elevation and blood streaked sputum. Unilateral wheeze was audible over the lower lobe of the left lung. X-ray films disclosed a mass in the left midlung field.

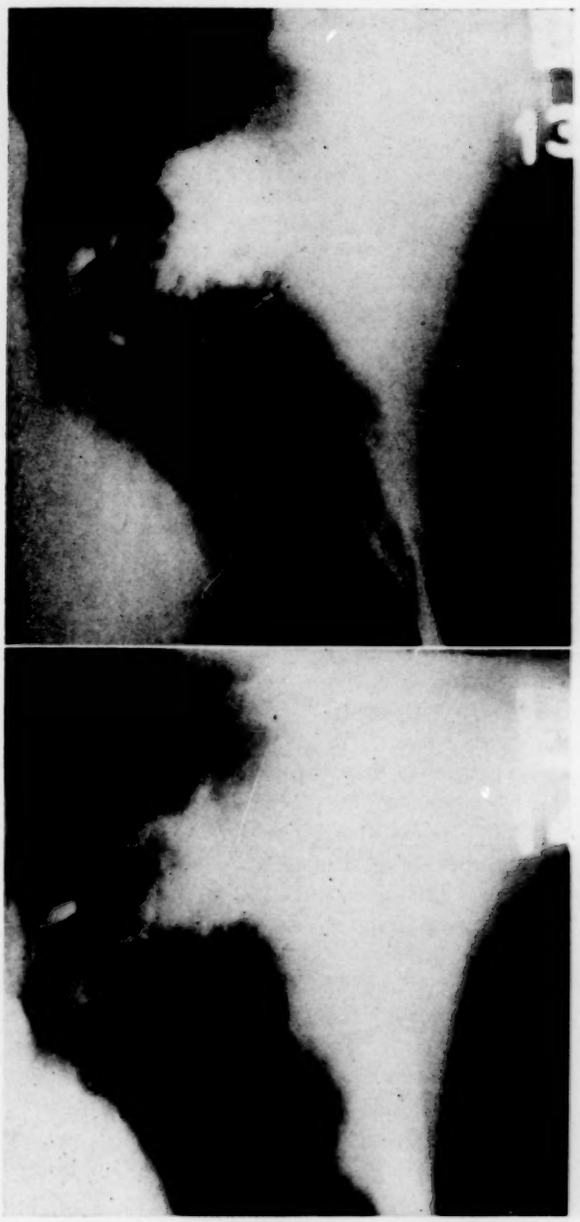


FIG. 7B. Tomograms showed a thick walled cavity suggestive of bronchial carcinoma. Left pneumonectomy was performed. Nocardia species was recovered from the specimen in pure culture and demonstrated in tissue. Patient remains well. All such patients should receive a postoperative course of sulfadiazine to preclude recurrence.

fact that pulmonary resection seems less frequently required in nocardiosis. The case of Connar et al. [*111*] illustrates the point that nocardiosis may occasionally resemble bronchial carcinoma and for that reason be subjected to thoracotomy. The need for postoperative chemotherapeutic coverage also is well illustrated by their patient, in whom empyema developed postoperatively. It was only then that the diagnosis was changed from lipoid pneumonitis to nocardiosis. On intensive sulfadiazine therapy the patient ultimately recovered. We have had two patients in whom chest roentgenograms suggested carcinoma. Following resection and postoperative sulfadiazine administration both went on to ultimate recovery.

Occasionally, pulmonary resection will be required to eradicate a residual nocardial lung abscess. Interestingly enough, the group that most frequently had to resort to surgery did not use sulfadiazine in any significant amount [*114*]. When nocardiosis and tuberculosis coexist, however, pulmonary resection is more likely to be utilized, as in the case of Hall and Cooley [*116*]. This was also true of our sole patient with the two coexisting diseases.

The value of surgical procedures outside the chest is well depicted by the patient of Bianco, Johnson, Martin and Nichols [*121*] who required extensive drainage and unroofing procedures of both lower extremities before overcoming the disease. Cerebral abscesses due to N. asteroides appear to have been cured by craniotomy both with [*122*] and without [*123*] ancillary sulfonamide administration, but as with nocardiosis

elsewhere, even when all gross evidence of disease has been resected an intensive course of therapy should probably be instituted to insure against recurrence.

SUMMARY

Actinomycosis and nocardiosis are closely related and often clinically indistinguishable diseases, chronic pleuropulmonary involvement, subcutaneous abscesses and multiple draining sinuses typifying both. Nevertheless they possess too many essential differences to be considered anything but two separate and distinct diseases. Especially important is the difference in therapy. Stated in the most elementary fashion, if one chooses to treat with penicillin all diseases caused by branching, fragmenting, filamentous fungi, then most patients with actinomycosis will recover, while almost all patients with nocardiosis will die.

The natural habitat of A. bovis is the human mouth; that of the nocardia is soil. Either can exist saprophytically in the oropharynx or respiratory tract, however, and mere recovery of the organism from sputum does not constitute absolute proof of the disease.

A. bovis is extremely sensitive to penicillin and for actinomycosis this constitutes the treatment of choice. The sulfonamides, although responsible for many earlier cures, show a far inferior inhibitory effect. *In vitro* sensitivity studies and clinical use have also shown that, depending upon strain sensitivity, one or another of the broad-spectrum antibiotics may be highly effective, so much so that undoubtedly some cases of very early actinomycosis are cured by random antibiotic therapy of seemingly minor infections without even suspecting the possibility of actinomycosis.

N. asteroides, the cause of most cases of systemic nocardiosis, is a relatively resistant organism, much less likely to be eradicated by indiscriminate drug administration. Perhaps this accounts for the growing importance of nocardiosis as opposed to the contrasting decrease in frequency of actinomycosis. All strains of nocardia that we have isolated have shown marked penicillin resistance. Sulfadiazine exhibits greater *in vitro* effectiveness and provides the best animal protection. More important still, its use in clinical nocardiosis has proved life-saving and has been responsible for practically every clinical recovery. The broad-spectrum antibiotics and streptomycin show a less marked and more variable inhibitory effect. Because of the extremely serious implications of most nocardial infections sulfadiazine is probably best combined with whatever drug appears most effective *in vitro*. Regardless of sensitivity tests, however, sulfadiazine should constitute the one essential component of any drug regimen for nocardiosis.

Basically, both actinomycosis and nocardiosis, like tuberculosis, are chronic diseases and a dramatic response to therapy should not be expected. Both diseases, but especially actinomycosis, produce a markedly fibrotic tissue reaction. This coupled with the tendency for organisms to accumulate in colonies in tissue (actinomycotic granules), makes it difficult to obtain effective drug levels in the areas of infection and within the compact granules themselves. Moreover, N. asteroides is notoriously resistant to all forms of therapy. Therefore, in both diseases the earlier treatment is instituted the greater the chance for cure. Chemotherapy must be continued in high dosage for prolonged periods if relapse is to be prevented.

The judicious use of surgical procedures such as drainage and resection is likewise indispensable in certain cases.

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Clinicopathologic Conference

Pulmonary Infiltration, Diarrhea, Weight Loss and Fever

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine, Preventive Medicine, and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient was a fifty-one year old white housewife who entered Barnes Hospital on April 27, 1959, with the chief complaint of fever of two weeks' duration. She died on April 29, 1959.

The patient had been in good health until approximately five years before admission at which time she noted the onset of moderately incapacitating lethargy and easy fatigability. Because of these symptoms she was seen by her family physician who told her that she probably had pernicious anemia and treated her with monthly injections of vitamin B_{12}. These were maintained over the ensuing four to five years without apparent symptomatic improvement.

In February 1959, following the death of a family member, she experienced an increased severity of her lethargy and fatigability; associated with this was the appearance of intermittent watery diarrhea, frequently with bright red blood and possibly mucus streaking the stools. She was hospitalized at a community hospital where the subsequent evaluation including gastrointestinal roentgenograms was entirely within normal limits. Following discharge she seemed to improve without specific therapy until two weeks before her admission to Barnes Hospital, when she became extremely lethargic, anorectic and experienced a recurrence of her gastrointestinal symptoms. She was readmitted to the community hospital where again the clinical and laboratory evaluation, including barium enema, proctoscopy and rectal biopsy, revealed no abnormalities. However, she was noted to be febrile and, because of the obscure nature of her fever, she was transferred to Barnes Hospital for further evaluation.

There had been a 30-pound weight loss since February 1959. The patient's appetite had been extremely poor throughout this time. There was no history of dyspnea, pain in the chest, abdominal pain or food intolerance.

Physical examination revealed the following: The patient was noted to be a pale, chronically ill white woman. The pulse was 90 per minute, respirations 32 per minute, temperature 38.7°C., and blood pressure 108/60 mm. Hg. There was slight pallor of the conjunctivas and mucous membranes. The upper respiratory tract and eye examinations were within normal limits. The neck was supple, and there was no venous distention. The thorax was symmetric and the lungs were clear to percussion and auscultation. The heart was not enlarged; the rhythm was regular; the tones were of good quality and there were no murmurs. The abdomen was flat and symmetric, without signs of fluid, or palpable organs or masses. The rectal examination and the neurological examinations revealed no abnormalities.

Admission laboratory data was as follows: The packed red cell volume was 38 per cent, white blood cells 13,800/cu. mm., basophils 2 per cent, juvenile forms 1 per cent, band forms 5 per cent, segmented forms 45 per cent, lymphocytes 43 per cent, and monocytes 4 per cent. The platelets appeared adequate. Urinalysis revealed specific gravity 1.021, reaction 4.5, 4-plus albuminuria, and was negative for reducing substances and microscopic examination of the urine sediment. Stool examination was within normal limits. Cardiolipin was not obtained. Blood urea nitrogen was 21 mg. per cent, fasting blood sugar 114 mg. per cent, sodium 125 mEq./L., potassium 4.6 mEq./L., chloride 89 mEq./L., and the carbon dioxide combining power 26.3 mEq./L. Stool culture was inter-

preted as showing a heavy growth of Escherichia coli and a moderate growth of alpha hemolytic streptococci. All agglutination reactions for salmonella were negative. Roentgenogram of the chest revealed a fine miliary mottling uniformly distributed throughout both lung fields. A calcified Ghon focus with calcification of the left hilar lymph nodes was noted in the left lung.

Repeat hemogram performed on the first hospital day showed a red blood cell count of 3.4 million/cu. mm., hemoglobin 11.2 gm. per cent, white blood cell count of 20,950/cu. mm. with band forms 3 per cent, segmented forms 71 per cent, lymphocytes 21 per cent, and monocytes 5 per cent. Hematocrit was 34 per cent, and the corrected sedimentation rate was 42 mm./hour.

The patient did not appear acutely or critically ill at the time of admission. Her temperature declined on the night of admission to normal levels, but subsequently rose to 39°c. during the ensuing twenty-four hours. Her respiratory rate remained approximately 30/minute throughout her brief period in the hospital, but she appeared only mildly dyspneic and was never cyanotic. Approximately twenty-six hours after admission she complained of nausea and had an emesis of 100 cc. of clear fluid. Subsequently she remained nauseated and somewhat dizzy. Blood pressure was noted to be 60/40 mm. Hg and she appeared slightly more dyspneic. Shortly thereafter her respirations stopped and she died.

CLINICAL DISCUSSION

DR. SOL SHERRY: The patient under discussion today presents a difficult problem in differential diagnosis and I doubt whether we can arrive at a correct diagnosis.

As you recall, our patient had two hospitalizations at another hospital, two months and two weeks before her only admission to Barnes Hospital. The records of the admissions, the rectal biopsy and her roentgenograms have been made available to us. The latter will be reviewed by Dr. Humphrey. Results of the rectal biopsy were reviewed by Dr. Lauren Ackerman. The specimen consisted of a portion of the mucosa and submucosa of the rectum; there was some hyperemia and evidence of increased mucous production but no other evidence of disease.

Additional information garnered from her records revealed that on her first admission she had a mild anemia, the stools were positive for blood, but the urine examination, chest roentgenogram and electrocardiogram were within normal limits. On her second admission, anemia was noted again; all three urine specimens examined then contained 3- to 4-plus proteinuria with a relatively normal urinary sediment; an intravenous pyelogram revealed no abnormalities; and an electrocardiogram revealed ST and T wave changes interpreted as anteroseptal myocardial ischemia.

Dr. Humphrey, would you review the roentgenograms for us?

DR. HARVEY A. HUMPHREY: A roentgenogram of the chest was the only examination we accomplished. It shows a well calcified primary complex in the lower lobe of the left lung and hilum. There was a slight exaggeration of the normal reticular pattern in the lung. There appeared to be an inflammatory infiltrate which was more pronounced in the bases than in the upper lobes. Lateral films showed fibrosis and nodulation in the upper lobes which I suspect was chronic reinfection pulmonary tuberculosis of minimal severity. The interpretation of these findings is difficult. This could be miliary tuberculosis, a miliary pneumonia of unknown etiology or it could be some interstitial fibrosis. A review of the roentgenograms obtained outside Barnes Hospital revealed the following: In February, examination of the chest looked quite normal. A gastrointestinal series was also performed at that time; this included a barium enema. The stomach, duodenum, jejuneum and ileum looked normal. In the colon, however, there was some loss of haustrations; there was also some slight serration in the outline. I think that these were the early stages of an idiopathic ulcerative colitis.

DR. SHERRY: What is your final diagnosis of the roentgenograms?

DR. HUMPHREY: Idiopathic ulcerative colitis and pulmonary infiltrate.

DR. SHERRY: Dr. Goldman, were you impressed with this pulmonary infiltrate?

DR. ALFRED GOLDMAN: It looked like a miliary lesion to me, not very striking, but nevertheless present, and I thought that I could also see something of the sort marked in the roentgenogram of the chest taken in February, so it would represent a progressive process since that time.

DR. SHERRY: What would you consider seriously in the differential diagnosis of the pulmonary lesion?

DR. GOLDMAN: A miliary lesion of the lung in

this geographic area suggests miliary tuberculosis or histoplasmosis. However there are many other lesions that can produce a miliary picture of this sort, many of which need not be mentioned. There have been as many as some eighty odd diseases described that may cause a miliary picture. In this case, a chronic granuloma would be my first choice. Acute diffuse interstitial fibrosis is also possible. We have no symptoms that would suggest this diagnosis except terminally. A collagen disease, I believe, should be included, because of the story of a long standing disease. A miliary picture in periarteritis is rare but may be present. The pattern usually is that of a changing type of roentgenographic picture rather than a miliary type. Bronchiolitis-fibro-obliterans should be mentioned. We have no history of inhalation of fumes of any sort, but the disease can occur as a result of chronic fibrosis of chronic lung lesions, such as bronchitis, asthma or influenza. Acute bacterial pneumonias can give you such a picture. It is rare, but one may see it with a staphylococcus or streptococcus, or even the salmonella organisms. I think we would have seen much more progressive disease since February if that were true. One should mention histiocytosis, but there is nothing else to substantiate the diagnosis.

DR. SHERRY: Then you believe we must give serious consideration to any number of diseases which cause a diffuse infiltration of the lung. Since this doesn't help too much, let us refer to the gastrointestinal tract. Dr. Scheff, what are your views about the nature of the lesion in this case?

DR. HAROLD SCHEFF: The story is very suggestive of a non-specific ulcerative colitis. However, the proctoscopic examination was essentially within normal limits except for a mild edema, and we know that in patients who have ulcerative colitis the most common site of involvement is the left side of the colon. The rectum and the sigmoid should have shown more definite changes than were actually seen. However, it still is a tenable diagnosis. I do think that this picture of the colon, or maybe small intestine too, could be compatible with some systemic infection. We have seen the same process go on in a patient with tuberculosis, with histoplasmosis and also patients with Hodgkin's disease.

DR. SHERRY: Our patient had a history of bloody stools for a two-month period. Would not one expect to find a more definite lesion if this were tuberculosis?

DR. SCHEFF: Yes, one would—tuberculosis, which is most likely a secondary infection, usually involves the small intestine, the terminal ileum and also the right side of the colon. It is conceivable you may have involvement of the left side, too, but most of the involvement is in the small intestine, Peyer's patches, and the cecum and ascending colon.

DR. SHERRY: What other types of disease should we seriously consider?

DR. SCHEFF: I would seriously consider a systemic disease that can produce secondarily a picture of ulcerative colitis. Any disease we mention, like histoplasmosis, tuberculosis or any granulomatous disease could produce the same picture.

DR. SHERRY: Then you would say that any type of disease which might infiltrate the colon could produce a picture of this sort, Dr. Scheff?

DR. SCHEFF: Yes, and I've seen exactly the same picture in patients who have neoplastic disease.

DR. BURTON SHATZ: In patients who present a picture compatible with idiopathic ulcerative colitis, other systemic diseases should also be considered such as amyloidosis and disseminated lupus erythematosus. Diarrhea may be a manifestation of some metabolic disturbance. For example, in Addison's disease, patients may have episodic diarrhea of a rather severe nature. The patient in discussion did have some of the symptoms suggestive of Addison's disease. For example, she had fatigability for five years, and death following an episode of hypotension with no evidence of hemorrhage. However, the elevated blood sugar, the absence of eosinophils, the admitting systolic blood pressure of 108 and the lack of pigmentation are, of course, all against this, and I do not consider this a very likely diagnosis in this case.

DR. SHERRY: What about blood streaking? I am aware that patients with Addison's disease may have bouts of diarrhea which may be followed by an overt crisis, but does one also observe blood streaking?

DR. SHATZ: In any patient who has diarrhea for a long period of time pre-existing lesions around the anal canal such as hemorrhoids or fissures may be caused to bleed and cause blood streaking of the stool.

DR. SCHEFF: We still have not considered very seriously the diagnosis of carcinoma in a patient that presented with diarrhea, mucus and blood.

DR. SHERRY: So far, we have established very little. Let us turn to the kidney where we have evidence of 4-plus proteinuria existing in this patient for the last two weeks of illness without much in the way of other changes in the sediment. Dr. Bricker, can you help us here?

DR. NEAL BRICKER: The available data are limited but do, I believe, offer some help. The presence of 4-plus protein in the urine during the patient's hospitalization at Barnes and also during a previous hospitalization suggests that the protein excretion was rather large. Obviously a qualitative concentration term cannot provide quantitative information about the twenty-four-hour excretion, but in general 4-plus proteinuria, even when the urine is concentrated, suggests that the twenty-four-hour excretion of protein is in excess of 2 gm. per day.

DR. SHERRY: The total urine volume on the first day of her admission here was 1,500 cc.

DR. BRICKER: Then it seems certain that the rate of protein excretion was in excess of 2 to 3 gm. per day. This suggests that the glomerular permeability to protein was increased, although this can occur without an intrinsic renal lesion (e.g., in congestive heart failure). I think that the evidence in this patient would favor an organic renal lesion. The presence of granular casts in the urine support this contention. In addition the patient's blood urea nitrogen was elevated suggesting that her filtration rate was decreased. In the absence of marked contraction of extracellular fluid volume, congestive heart failure and other edema-forming stimuli, a decrease in filtration rate particularly in association with proteinuria and granular casts, is consistent with an organic renal lesion. The magnitude of nephron destruction could not have been marked however for several reasons. First, the absolute elevation of urea nitrogen was small; secondly, she was still able to concentrate her urine, even correcting for the amount of protein in the urine; and thirdly, the intravenous pyelograms showed a normal ability to excrete and concentrate the dye. Therefore, with regard to the nature of the lesion, I think we can say that it was intrinsic to the kidney, was characterized by some nephron destruction, with increased glomerular permeability, without hematuria in the residual functioning nephrons; and that it may either be related to her underlying disease, or totally coincidental. Amyloidosis has been mentioned. I think this could give the picture we see in this patient.

DR. SHERRY: Then you would conclude that some kind of infiltration disease could produce this renal picture, or that it might be due to an incidental renal disease which she may have had.

DR. BRICKER: Yes, I think that's a fair statement.

DR. SHERRY: Dr. Recant, there have been some recent attempts to relate extensive proteinuria with anatomical changes in the nephrons. Would you comment on the current status of these observations?

DR. LILLIAN RECANT: The introduction of the electron microscope in the study of experimental and clinical nephrosis has permitted the description of a specific glomerular lesion which is associated with the presence of significant proteinuria. This lesion resides in the podocyte cell of the glomerulus. This cell is an epithelial cell which separates glomerular capillaries from Bowman's space. It has foot processes which are regularly arranged against the filtering surface, so that filtration from the capillary lumen to Bowman's space must be either through or between these structures.

The association of changes in this cell with proteinuria stem from the following observations: First it has been demonstrated that the new-born infant or animal has a physiologic proteinuria. These fetal animals and newborn rats have incompletely developed podocytes and the foot processes have not yet been arranged in an orderly pattern. Secondly, recent reports have appeared of congenital nephrosis, a very rare disease which has been described in several members of a family. In this disease, the nephrosis is present at birth and it has been found that there may be a total absence of the foot processes. Thirdly, when you produce an experimental nephrotic syndrome, whether you do it with aminonucleoside, or antikidney serum, or any other method, you find progressive change in this podocyte cell, particularly in the foot processes, which become large and fuse over the filtering surface. Finally, in our studies with Dr. James Harkin, we demonstrated that prior to the development of proteinuria, in the experimental production of nephrosis, changes occurred in these foot processes. This adds up to a picture that associates the integrity of the foot processes of the podocyte cell with the absence of proteinuria and vice versa.

DR. SHERRY: Perhaps our diagnostic considerations would be helped by an explanation

of the terminal event. Dr. Smith, what caused her sudden death?

DR. JOHN R. SMITH: The circumstances of sudden death are often difficult to unravel from the circulatory viewpoint because the cessation of circulation from various causes give rise to many similar signs. Sudden death of the kind described here is frequently the result of one or more pulmonary emboli. On the other hand, as death was preceded by nausea and vertigo, it is possible that extreme disturbance of the central nervous system (affecting especially the autonomic system) may have occurred. The causes for such an event may also have been many, including intracranial hemorrhage or abscess.

DR. SHERRY: Do not our neurological colleagues usually point out that although neurological disorders frequently terminate fatally, they are usually not associated with sudden death?

DR. SMITH: Yes. This is true except for vascular accidents or perhaps edema occurring in and around the brain stem, by which life may be terminated very suddenly by the disruption of vital processes.

DR. SHERRY: You do not believe that death in this patient could have occurred from cardiac origin, with acute heart failure?

DR. SMITH: I am inclined to think that death was not of cardiac origin in this case.

DR. SHERRY: Dr. Daughaday, I was impressed by the symptoms of languor and fatigability, hypotension, and low serum sodium and chloride levels. Could death in this patient have been caused by the adrenal insufficiency?

DR. WILLIAM DAUGHADAY: The situation as you describe it, is entirely compatible with adrenal insufficiency, but it is also paralleled of course, in the number of chronic severe granulomatous diseases. Dr. Shatz' differential diagnosis is very good and I would agree with him entirely. The absence of pigmentation is most unusual in long standing Addison's disease and it raised the thought in my mind that actually this might be hypoadrenalism secondary to pituitary disease. Is there any information available about this woman's menstrual and reproductive history? Is there any suggestion at all that she might have had a pituitary infarction because unexplained anemia, lethargy and fatigue is common in panhypopituitarism.

DR. SHERRY: I know that she had perfectly normal pregnancies which were uncomplicated.

DR. DAUGHADAY: This information would make hypopituitarism unlikely, but I don't have enough data to reject the possibility entirely.

DR. SHERRY: It seems to me that an adequate diagnosis in this case should explain the following features: weakness and probably anemia of five years' duration; intermittent diarrhea with occasional blood streaking, weight loss and debility of two month's duration; recent onset of fever, pulmonary infiltration, and 4-plus proteinuria terminating in sudden death. These features appear to me to be most reasonably explained by a protracted systemic disease, infiltrating the lungs, kidneys, gastrointestinal tract, possibly the hematopoietic system, the heart and the adrenals. The differential diagnosis most seriously to be considered includes: a granulomatous disease either on an infectious or noninfectious basis, some disseminated neoplastic disease; diffuse vascular disease; or some metabolic type disorder such as amyloidosis. Dr. Harford, what infectious granulomatous disease could explain this entire picture?

DR. CARL HARFORD: Although we have all agreed that there is not enough evidence to make a diagnosis, I think that the previously mentioned possibilities of tuberculosis and histoplasmosis are good ones. The presence of a miliary lesion in a patient who lived in this area and some evidence of an adrenal lesion are suggestive of histoplasmosis. In this connection I should like to point out that Dr. Pinkerton has described at least one case of histoplasma infection of the colon.

DR. SHERRY: If a person had disseminated histoplasmosis, active enough to give bloody diarrhea for a period of two months, wouldn't this person have had fever during the entire period of time?

DR. HARFORD: I should think so.

DR. SHERRY: And what about the 4-plus proteinuria? Would this be explainable on the basis of histoplasmosis?

DR. HARFORD: I should doubt that it could be explained directly but I think the amyloid suggestion is a worthwhile one.

DR. SHERRY: You mean histoplasmosis complicated by secondary amyloidosis?

DR. HARFORD: Yes.

DR. SHERRY: Dr. Vavra, what types of noninfectious granulomas could give rise to a syndrome of the type exhibited by our patient?

DR. JOHN VAVRA: There are several noninfectious granulomas which should be con-

sidered in this patient, but none of them appear to be the most likely diagnosis. Sarcoidosis may produce a clinical picture of fever, a miliary pulmonary infiltrate, and weight loss. The absence of other clinical features of sarcoidosis including uveitis, parotid enlargement, lymph node enlargement, hepatosplenomegaly, skin lesions, and bone lesions in a patient with illness of this severity would be unlikely. Sarcoidosis does not usually produce as many symptoms referrable to the gastrointestinal tract as the patient showed. Renal involvement on the basis of sarcoid is usually due to hypercalcemia and resulting nephrocalcinosis and thereby produces a more abnormal urinary sediment than was found. When sarcoid leads to sudden death it is usually a consequence of severe cardiopulmonary disease and of invasion of the myocardium with granulomas. These patients often have congestive failure prior to death. These features do not fit the terminal course of our patient.

Chronic beryllium poisoning may lead to a picture of chronic pulmonary granulomatosis with features of progressive pulmonary insufficiency. The lack of known exposure and clinical course make this diagnosis extremely unlikely.

One might consider the possibility of Wegener's granulomatosis as a non-infectious granuloma. This disease may first appear as a nodular and miliary infiltrate in the lung due to a necrotizing and granulomatous vasculitis. The patients are usually quite ill and run a rapidly progressive course. By the time death occurs the patients usually have other findings which our patient did not clearly demonstrate. These findings include pancreatitis and ulcerative lesions of the upper respiratory tract which can be observed clinically, and there may be extensive granulomatous involvement of other organs. Renal involvement is of the form of a glomerulitis with more abnormal urinary sediments than our patient showed. Death is usually a result of renal failure.

DR. SHERRY: From time to time we have overlooked a disseminated histiocytosis. Would you consider this disease as a non-infectious granuloma and could it stimulate the clinical picture described here.

DR. VAVRA: The fact that we have been fooled in the past should make us at least consider the diagnosis in any patient with a generalized and bizzare illness. The disseminated histiocytoses are characterized by proliferation of histiocytic elements in localized areas or widely disseminated through the body. The clinical picture, the course of the disease, and the prognosis are extremely variable, making classification difficult, but the clinical picture has been divided into three categories depending on the predominance of certain features. These include eosinophilic granuloma, Schüller-Christian disease, and Letterer-Siwe disease. Pulmonary lesions and gastrointestinal symptoms may be present, however most patients have other symptoms and findings which our patient did not have. These include localized tumor masses, often in bones, diabetes insipidus due to histiocytic proliferation in the region of the hypothalamus, hepatosplenomegaly, lymph node enlargement, exophthalmus, and chronic otitis media. I would think this group of diseases unlikely in our patient.

DR. SHERRY: Can a disseminated histiocytosis run a low grade protracted course and then accelerate into a rapid course with an acute death?

DR. VAVRA: The histiocytosis may run a protracted course, but when sudden death occurs it is usually precipitated by a severe infection and not an acute flare-up of the disease.

DR. SHERRY: I gather than that you believe a non-infectious granuloma unlikely and consider an infectious granuloma a more likely possibility.

DR. VAVRA: Yes, I would favor a disseminated infectious illness, probably tuberculosis, over any of the possibilities I have mentioned.

DR. SHERRY: Dr. Reinhard, would you consider the possibility of a disseminated neoplastic disease?

DR. EDWARD REINHARD: I think that this is a very distinct possibility here and I would put neoplastic disease as the number one possibility on my list of diagnostic possibilities. There are no localizing symptoms or signs to point to any specific organ as the site of origin of a malignant tumor, but I think the patient may well have had carcinomatosis, the primary tumor being, perhaps, quite insignificant.

DR. DAUGHADAY: One of the few hints we have in the physical examination was the tachypnea. Was this sustained?

DR. SHERRY: Yes.

DR. DAUGHADAY: This is quite characteristic of diffuse metastatic involvement of the lung.

DR. SHERRY: Would not tachypnea be likely to occur in all diseases which extensively infiltrate the lungs?

DR. DAUGHADAY: More characteristic of neoplastic than, say, sarcoid.

DR. SHERRY: Dr. Moore, do you believe that we must give serious consideration to a diffuse vascular or connective tissue disorder?

DR. CARL MOORE: No. Vascular disease would be a most unlikely possibility. It would be difficult to explain everything on the basis of lupus. This is also true of polyarteritis in the absence of hypertension and eosinophilia, and with such extensive involvement of the lungs.

DR. SHERRY: Dr. Eisen, let us consider the possibility of amyloidosis since a number of features of this case suggest this diagnosis: the presence of bloody diarrhea; involvement of the kidney with prominent proteinuria; the long course; and the infiltration of a number of organs. First, how do you characterize amyloidosis?

DR. HERMAN EISEN: The disease is characterized by deposits in the interstitial tissues of rather homogeneous hyaline-like deposits with special staining characteristics.

DR. SHERRY: What is known about the chemistry of the amyloid material?

DR. EISEN: There have been a number of analyses of amyloid deposits, especially those that occur secondary to chronic tuberculosis. The material is largely protein. At least some of it is gamma globulin as judged by staining reactions with fluorescent antigamma globulin antibodies. Polysaccharides are also present and, in fact, are responsible for the name given to these deposits. The polysaccharide component has recently been pretty well characterized by Karl Meyer and his associates. It turns out to be a very unusual acid mucopolysaccharide, whose composition is very much like that of heparin. It is a highly sulfated material and is being referred to now as heparitin.

DR. SHERRY: The pathologist usually distinguishes between primary and secondary amyloidosis on the staining quality of the deposits and their sites of deposition. Do you agree with this or do you believe that the best differentiation is an etiological one, that is, if there is a good cause for the amyloidosis than it is secondary; if there is not, then we must consider it as primary.

DR. EISEN: The anatomical basis for classifying amyloid is usually satisfactory. But there are many instances in which the anatomical distribution of amyloid can be misleading. For example, the amyloid which sometimes occurs without associated suppurative diseases can on occasion have a distribution just like that seen in the amyloid which occurs typically in association with destructive tuberculous lesions.

DR. SHERRY: Do you believe we are dealing with a case of amyloidosis and, if so, what type?

DR. EISEN: Most of the features which you listed before are consistent with amyloid disease of the so-called primary type; namely, the long course, the severe lethargy and fatigability, the gastrointestinal symptoms with diarrhea and bleeding and the proteinuria. In fact, the only thing I believe to be inconsistent is this patient's fever. If it does turn out that she had amyloidosis, which I think is a long shot diagnostically, I would assume the fever would have some other cause.

DR. SHERRY: Then you believe this patient's clinical picture is entirely compatible with primary amyloidosis; however its rarity and the presence of fever lead you away from the diagnosis.

DR. EISEN: Yes, one other thing should be mentioned. This is the fact that the biopsy specimen did not reveal amyloid deposits. This is significant if the biopsy specimen was taken from an area in which there was a bleeding lesion.

DR. SHERRY: The biopsy specimen was taken from an area where there was hyperemia, but it was a fairly superficial biopsy and no arterioles were seen.

DR. EISEN: It's a small point against the diagnosis.

DR. SHERRY: A poll of the audience (faculty, students, and guests) reveals that 50 per cent favor an infectious granuloma, either tuberculosis or histoplasmosis; nobody favors a noninfectious granuloma; 15 per cent favor a neoplastic disease which has disseminated widely from an unknown primary site; about 3 per cent favor a diffuse vascular or connective tissue disorder; and approximately 5 per cent favor amyloidosis either primary or secondary. The rest did not vote.

PATHOLOGIC DISCUSSION

DR. HIDESHIGE IMAI: The heart was of normal size, but the right ventricle showed slight hypertrophy. A close-up view of the heart showed waxy pallor of myocardium, especially near the atrial ventricular ring and under the endocardium. In the endocardium of the atrium (Fig. 1.) there were numerous waxy translucent globules and blotches. The lungs appeared



FIG. 1. Gross photograph of the left atrial endocardium showing transparent waxy globules of amyloid deposited subendocardially.



FIG. 2. The increased rigidity of the lungs can be seen by the sharp angle the cut surface forms with the pleura, *left*. Innumerable nodules of translucent amyloid are apparent on the cut surface and beneath the pleura.

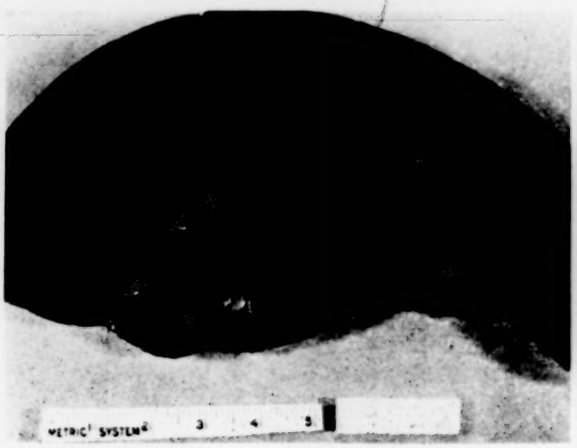


FIG. 3. Gross photograph of the spleen showing the dry waxy appearance of the cut surface.

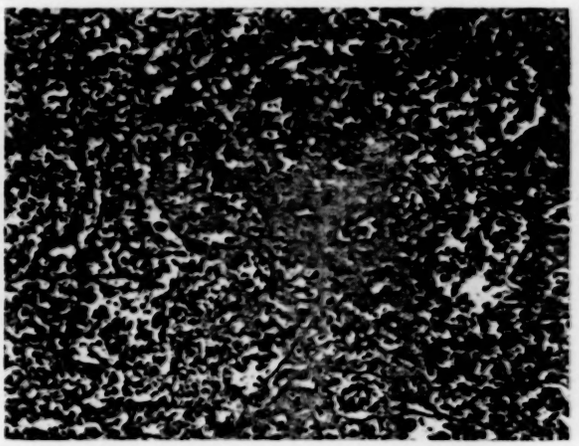


FIG. 4. Photomicrograph of the spleen; hematoxylin and eosin, magnification × 100. Lymphoid follicles, right and lower left are small. The red pulp is diffusely infiltrated by amyloid.

abnormally rigid. They weighed 1,430 gm. together, moderately heavier than usual. No pulmonary embolus was found. In the lower lobes (Fig. 2) there were multiple small nodules composed of waxy translucent material, and alveolar septums were thickened by the same material. The same nodular deposits were seen on the pleural surfaces. The liver was of normal size and normal except for prominent lobular markings due to pale central areas. The spleen was enlarged, weighing 450 gm., and was very firm although pliable. On the cut surface, the spleen was dry, homogeneously waxy, and deep red. (Fig. 3.) The kidneys were enlarged weighing 400 gm. together. The only remarkable feature was the pallor of the cortex. The mucosa of the stomach, ileum and large intestine was congested, edematous, and bore multiple petechiae. Cultures taken from the ilium revealed a profuse growth of E. coli and Staphylococcus aureus. The bone marrow of the vertebra, sternum and ribs was red and hematopoietic; femoral marrow was a mixture of yellow fatty and red hematopoietic tissue.

DR. JOHN KISSANE: As you may have surmised from the description and illustrations of the gross lesions, particularly those in the spleen, heart and lungs, this is a case of primary systemic amyloidosis. The involvement in this case was typical in the spleen and heart, but very unusual in the extent of involvement of the lungs, although even here, the involvement was histologically and tinctorially typical. There were, in addition to these sites, microscopic

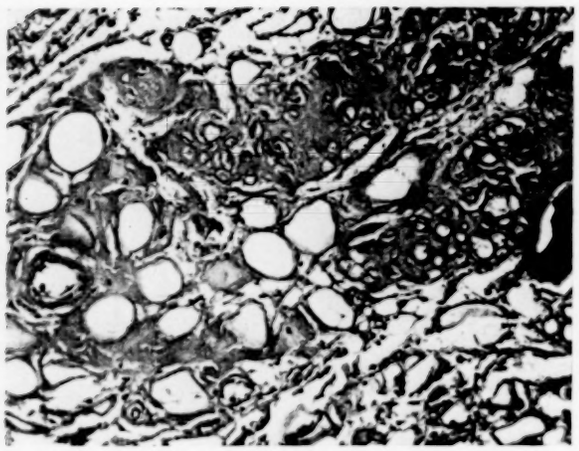


FIG. 5. Photomicrograph of myocardium; hematoxylin and eosin, magnification × 100. Perimysial rings of amyloid and confluent interstitial deposits are evident.

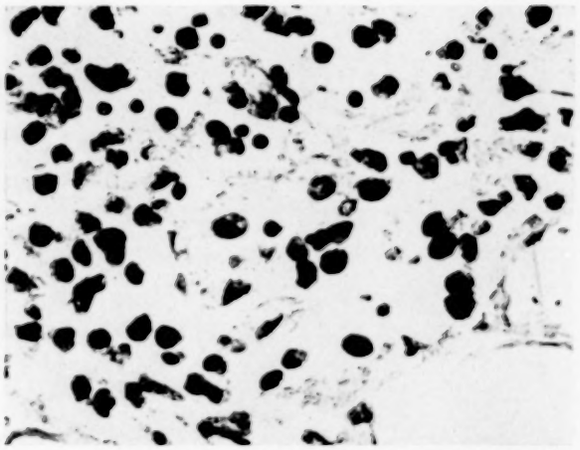


FIG. 6. Photomicrograph showing a focus of interstitial inflammatory cells in the right ventricular myocardium; hematoxylin and eosin, magnification × 370. Many plasma cells are recognizable.

lesions in the kidneys, liver, pancreas, adrenals, retroperitoneal connective tissue and in the muscularis and blood vessels of the gastrointestinal tract.

In a section of the spleen, stained with hematoxylin and eosin (Fig. 4), one sees depleted, compressed remnants of lymphoid follicles. The red pulp is virtually obliterated by clouds of amorphous, eosinophilic, structureless material. This distribution of amyloid, primarily in the red pulp and compressing the lymphoid follicles is characteristic of the primary form of amyloidosis. In the secondary form, splenic involvement often appears to have begun in the lymphoid follicles and to spread into the red pulp along the sinusoidal reticulum.

In the right ventricular myocardium, small shrunken myofibrils were enclosed in circles of the same material that was present in the spleen. (Fig. 5.) The myofibrils encased in the amyloid showed varying degrees of retrogressive changes, ranging to complete atrophy with resulting confluence of amyloid in confluent interstitial deposits. Another feature which was present in the right ventricular myocardium in this case, and is present in occasional cases of amyloidosis of any type, was a focal inflammatory reaction, rather pleomorphic in character but with considerable numbers of recognizable plasma cells in the inflammatory infiltrate. (Fig. 6.) This finding does not indicate that this is a case of amyloidosis secondary to myeloma, although one must always search for features of myelomatosis, none of which was present in this case. A low-power photomicrograph shows the extent of amyloid deposition in the myocardium stained with Congo red. I might say that the tinctorial properties of amyloid have been the subject of many publications and are of some use in distinguishing the primary from the secondary form. As Dr. Eisen mentioned, there is considerable overlapping in anatomical distribution of lesions in the various forms. It is claimed that in tinctorial properties, the amyloid in the primary form of amyloidosis is more quixotic and tends to vary more than in the secondary form of amyloidosis or amyloidosis complicating multiple myeloma. The name para-amyloidosis has been suggested for cases of primary amyloidosis in which the amyloid stains atypically.

The next slide (Fig. 7) is a low-power view of a subpleural area of the lung. These lungs were massively involved. We were surprised that this patient manifested so few respiratory symptoms. The interlobular and interalveolar septums are diffusely thickened. Higher magnification (Fig. 8) showed the character of the interstitial deposition. In the interstitial tissue, often perivascularly, are billows of amyloid which form focal nodules often containing considerable numbers of foreign body giant cells. The occurrence of a foreign body reaction about deposits of amyloid is somewhat more characteristic of the solitary, nodular form of amyloidosis which is fairly common in the upper respiratory tract, but it also occurs in the other forms of amyloidosis.

A spectrum of changes can be seen in the kidneys of this case. Most glomeruli reveal diffuse thickening of the glomerular basement membrane, but a few glomeruli display a tendency to nodular concentrations of amor-

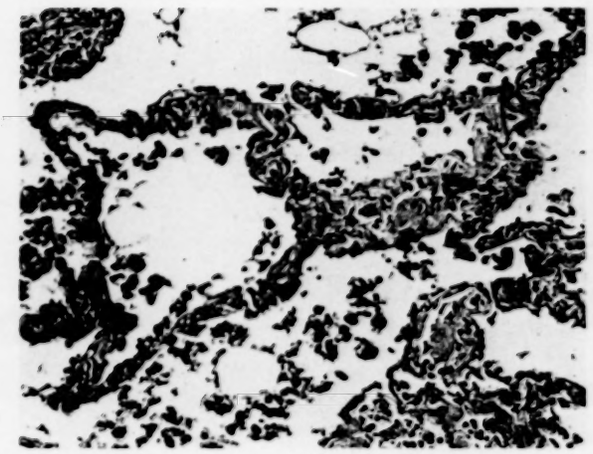


FIG. 7. Photomicrograph of the lung; hematoxylin and eosin, magnification × 100 showing the deposition of amyloid in interalveolar septums.

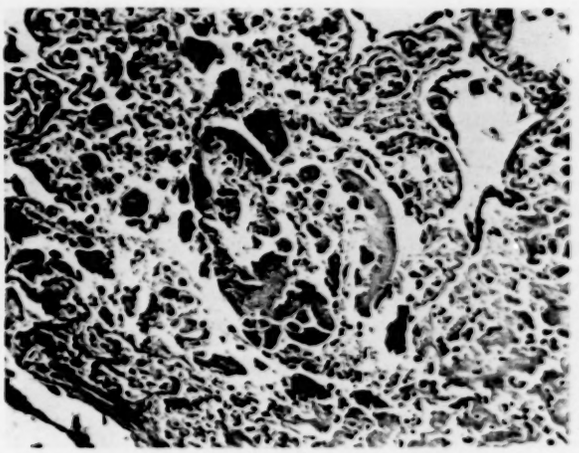


FIG. 8. Photomicrograph of lung; hematoxylin and eosin, magnification × 100 showing a foreign body reaction about a fragmented mass of amyloid.

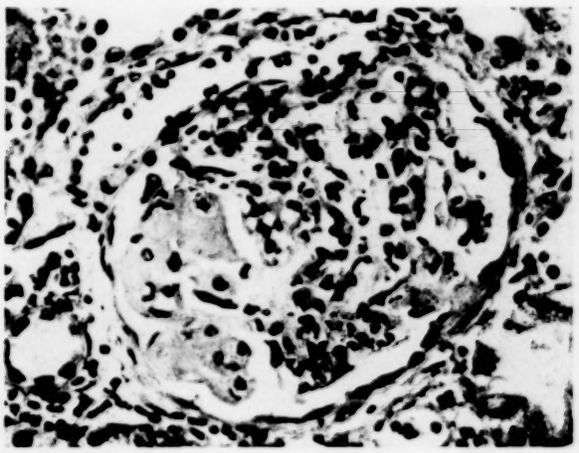


FIG. 9. Photomicrograph; hematoxylin and eosin, magnification × 225 showing a renal glomerulus with focal nodular accumulations of amyloid.

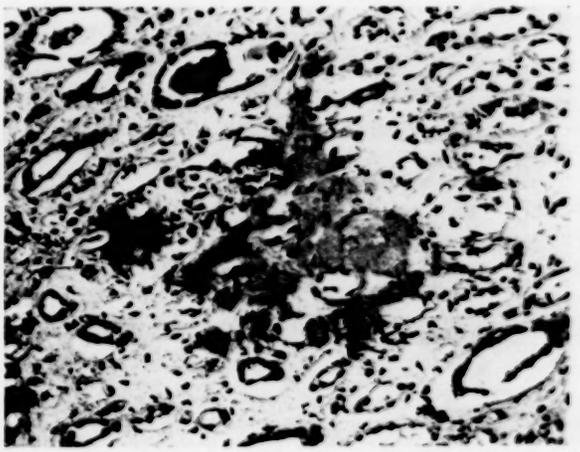


FIG. 10. Photomicrograph; hematoxylin and eosin, magnification × 100 showing a focus of amyloid deposition in the renal medulla.

phous eosinophilic material. (Fig. 9.) In the renal medulla, the deposition of amyloid is more striking as flame-shaped, non-circumscribed aggregates around capillaries, small venules, and also around tubules. (Fig. 10.) The only involvement of the liver was focal deposition of amyloid in the wall of larger branches of the portal vein, another feature which tends to differentiate this case of amyloidosis from the secondary form in which sinusoidal involvement of the liver is the rule.

Similar nodular accumulations of amyloid were seen in and around small vessels in the pancreatic connective tissues. Small irregular deposits of the same material are present in the interstitial tissue in the stratum fasciculas of the adrenal. The amount of adrenal tissue so involved was really minimal and in no way

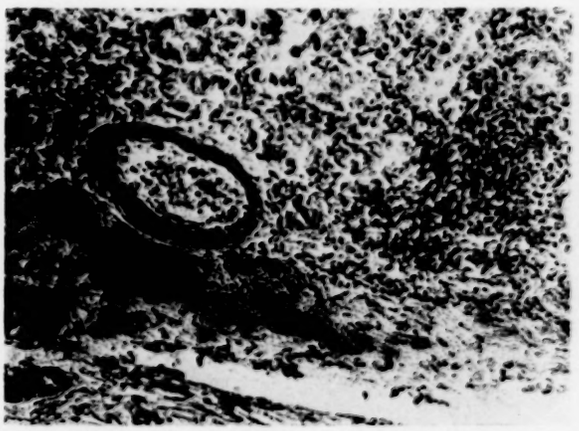


FIG. 11. Photomicrograph of a frozen section of stomach stained with Congo red; magnification × 100. Amyloid is present in the wall of the blood vessel and replaces much of the muscularis (dark grey in the photomicrograph).

sufficient to support histologically the suggestion of hypoadrenalism in this case. A section of the periadrenal adipose tissue reveals still another feature of primary amyloidosis, that is the formation of the so-called "amyloid rings" which are particularly conspicuous in the retroperitoneal and epicardial fat.

Involvement of the gastrointestinal tract in this case was rather extensive microscopically, although sections stained routinely were not impressive. Methyl violet, and especially Congo red (Fig. 11), however, revealed unexpectedly extensive replacement of the muscularis of the stomach and intestine by amyloid in addition to amyloid infiltration in the walls of small blood vessels. It is the only anatomical finding relevant to this patient's gastrointestinal symptoms. We can offer no anatomical explanation for sudden death.

Pathological diagnoses are: diffuse primary amyloidosis involving the lungs, heart, retroperitoneal connective tissue, spleen, kidneys, diaphragm and psoas muscle, lymph nodes, adrenals, muscularis and blood vessels of the stomach and intestines, interstitial tissue of the pancreas, and blood vessels of the liver; hypertrophy of the right ventricle (5 mm.); congestion and petechiae of the mucosa of the stomach, ileum and colon and the mucosa of the renal pelves and calyces; hyperplasia, predominantly erythroblastic, of the bone marrow, including that of the femur; congestion of the liver.

Case Reports

Fatal Nephritis in Chronic Phenacetin Poisoning*

SYLVAN E. MOOLTEN, M.D. *and* IVAN B. SMITH, M.D.
New Brunswick, New Jersey *Dayton, New Jersey*

PHENACETIN resembles aspirin in its properties as an analgesic and antipyretic, and is customarily prescribed together with aspirin in combinations with codeine, caffeine, amphetamine, antihistaminics or barbiturates. The advantage of such combinations probably lies in the fact that the dose of each constituent is kept well below its toxic level. A favorite combination, caffeine, phenacetin and aspirin, is marketed directly to the public under various trade names.

The health hazard of phenacetin is known to be much less than that of acetanilid, although in their toxic effects the two compounds are regarded as indistinguishable [*1,2*]. The use of acetanilid-containing nostrums has declined greatly, probably because of publicity regarding harmful effects of the drug. Phenacetin, however, continues to enjoy a good reputation and the potential danger of excessive use has aroused little public concern.

The medicinal abuse of phenacetin is common in persons who regulate their own dosage of proprietary drugs for relief of recurrent headache or musculoskeletal pain. It is often taken for an emotional "lift," particularly in its combination with caffeine or amphetamine. Most persons are able to tolerate surprisingly large daily doses for long periods with little or no apparent harm. Those who display toxic effects are apparently quickly relieved when the drug is withdrawn. The toxic effect which is perhaps known best to the physician is its action on hemoglobin, which results in formation of methemoglobin, sulfhemoglobin and other oxidation products [*1–3*]. Because this effect is largely reversible it gives rise to little or no anxiety and is regarded more in the light of a medical curiosity of importance chiefly in the differential diagnosis of cyanosis unexplained by other causes. Many cases of drug-induced methemoglobinemia and sulfhemoglobinemia undoubtedly escape detection when the cyanosis is inconspicuous or is dismissed as "muddy complexion" [*3*]. Its dirty gray-violet hue has been likened to the appearance of a healthy person observed under the mercury vapor lamp. Part of this effect may be due to brown derivatives of para-aminophenol formed in the degradation of the drug. Other symptoms which identify phenacetin habituation, such as persistent headache, debility and nervous irritability, may be ascribed by the unsuspecting clinician to constipation or psychoneurosis. Instances of serious harm to the brain or other organs have seldom been recorded; Espersen's case of fatal chronic phenacetin poisoning was associated with sulfhemoglobinemia and hepatic cirrhosis [*4*]; Askari and Hodas reported a case of sulfhemoglobinemia in a young woman during pregnancy whose child died one month after birth of degenerative encephalopathy [*5*].

Beginning with the paper of Spühler and Zollinger [*6*] in 1953, reports have appeared in the Swiss medical literature demonstrating the menace of chronic phenacetin poisoning in a new and more dangerous aspect related to harmful effects on the kidneys [*6–9*]. In several instances these effects were manifested by uremia, which was often fatal. The significant renal findings at autopsy were chronic inflammation and scarring associated with widespread destruction of convoluted tubules. The blood vessels and glomeruli were comparatively unaffected. Necroses of the papillae were common. The disorder of the kidney was classified by these writers as "chronic interstitial nephritis" since the primary lesion was interstitial inflammation followed by scar tissue proliferation. Tubular damage was be-

* From the Middlesex General Hospital, New Brunswick, New Jersey.

lieved to occur secondarily. The scanty cellular exudate, mostly lymphocytes, and the abundant fibrosis appeared to be consistent with the gradual and insidious clinical progression of the disease. In most instances the onset and advance of the disease were unrecognized until its final stages. Repeated examination of the urine disclosed little or no abnormality; in some instances there was a slight degree of albuminuria and a few leukocytes and red cells in the sediment. As a rule there was no elevation of blood pressure until late in the course of the disease. The earliest and most consistent warning of impairment of the kidneys was increasing polyuria caused by loss of their concentrating ability. Later there was reduction in urea clearance. As the disease progressed, occasional disturbances in mineral metabolism were seen such as the salt-losing syndrome, nephrocalcinosis and osteoporosis. Inulin/para-amino-hippuric acid clearance ratios, determined in a few cases, were altered from 1:5 to values approaching 1:2, in further evidence of selective impairment of tubular function [*6*].

The danger of renal complications impelled Moeschlin [*9*] in Switzerland to recommend legislation requiring that phenacetin be obtainable only by prescription. In a summary (1957) of his personal observations during a two-year period at the Soluthurn Municipal Hospital he tabulated fifty-seven cases of chronic phenacetin abuse among two thousand four hundred and twenty admissions, an incidence of nearly twenty-four per thousand patients. Nine of the fifty-seven patients had evidences of "chronic interstitial nephritis" with azotemia—an incidence of almost four per thousand admissions. Four of the nine died; the remaining five recovered on withdrawal of the drug with or without the aid of peritoneal dialysis. In the group of patients who recovered, the intake of phenacetin was calculated to have ranged between 2.7 and 10.96 kg. over periods of five to twenty years, taken at the rate of five to fifteen tablets a day. One of these patients, who declared that she had been taking no more than two to five tablets a day, totalling 6.5 kg. at the end of twenty years, had a blood urea level of 351 mg. per cent. Another, with a blood urea level of 370 mg. per cent, confessed taking a total of 9.1 kg. in ten years. In the others the blood urea levels ranged between 43 and 217 mg. per cent. In the group of four patients who died the total admitted consumption of phenacetin was comparable with that of the five who recovered, although the daily intake was somewhat higher (about ten to twenty-five tablets a day). In the fatal cases the blood urea levels ranged between 120 and 223 mg. per cent.

No report of phenacetin nephritis occurring in this country has appeared thus far in the literature. That it exists, latent or manifest, can hardly be doubted when the circumstances are considered which favor prolonged overdosage of the drug in certain types of personalities, particularly psychoneurotics over-inclined to self-medication. Modern technics of advertising must share part of the blame for the increasing use of phenacetin preparations. The public is besieged with persuasive sales promotion advice to buy "over the counter" drug combinations containing phenacetin.

More serious, perhaps, than lack of sales resistance is the danger of habituation which arises out of the peculiar property of phenacetin to produce severe headache when taken repeatedly in large doses [*2,8,9*]. Nervous irritability, depression, tremor, muscular weakness and mental debility are commonly associated with phenacetin-induced headache. As a result the compulsion may easily develop in predisposed persons to continue to take the drug for relief of the very symptoms caused by it. Mental confusion which results also from the drug may cause such persons to grow increasingly careless about dosage and to swallow the tablets without regard for their number. This type of vicious cycle often underlies habitual abuse of the drug and constitutes an entrapment which differs from addiction in the fact that the taking of the drug rather than its withdrawal creates the condition which compels its continued use. It is generally believed that addiction as such does not occur [*1,2*]. Nevertheless, phenacetin habitués resemble narcotic addicts in the secretiveness with which they surround their compulsive use of the drug and in their obstinate refusal to turn to other forms of relief for their symptoms. It is hardly surprising, therefore, that the physician gropes vainly for the diagnosis unless he is alerted by the patient's cyanosis or by chance discovery of the tablets.

CASE REPORT

M. R., a housewife thirty-four years of age at the time of her death, was first treated by one of us (I. B. S.) five years previously for threatened abortion

of her third pregnancy. Five months later she was delivered of a healthy baby.

At the time of her first visit she mentioned that she had been suffering from severe headaches for several months before the beginning of this pregnancy. The headaches were described as occurring daily, usually unilaterally, either on the right or left side, non-throbbing and unassociated with visual or other phenomena. Because of their obstinate and peculiar nature she was examined at a large headache clinic in a hospital in New York City where the headaches were held to be "vascular" in origin. The headaches persisted despite prescribed treatment and remained a prominent symptom throughout the entire subsequent course of her illness. From the onset of her illness she also had more or less persistent anorexia associated with periodic nausea and vomiting (especially at night), and a steady loss of weight. When she was seen six weeks postpartum her weight loss had totalled 21 pounds. Nine months later she had repeated epigastric pains and vomiting for a period of three weeks. Two years before her death she had lost almost 30 pounds and appeared extremely nervous and irritable. The presence of fine tremor, a slight lid-lag and stare prompted examination for hyperthyroidism. The basal metabolic rate was plus 21 per cent but the radioiodine uptake was 30 per cent of the total dose, considered within the normal range. As a therapeutic test the patient was given propylthiouracil for a few weeks but showed no improvement.

Shortly afterward severe abdominal pain developed. It was centered in the left hypochondrium radiating into the left shoulder but eventually spread over the entire abdomen. She also had marked nausea and vomiting. The symptoms suggested acute pancreatitis and the patient was admitted to the Middlesex Hospital. Laboratory tests and other findings failed to confirm this diagnosis. Eventually an orange-sized mass presented to the left of the umbilicus and was drained of a large amount of foul-smelling pus. The "flat film" of the abdomen at that time showed evidences of peritonitis and ileus together with free air under the left diaphragm. She improved rapidly, and subsequent roentgenographic study of the gastrointestinal tract showed no intrinsic disease although air was still detected under the diaphragm. The gallbladder series was within normal limits.

Two months after the first admission the patient was readmitted with severe abdominal pain which radiated again into the left hypochondrium and back, again suggesting pancreatitis or peripancreatitis. Serum amylase levels were within normal limits. The intravenous pyelogram showed no abnormal findings in the kidneys and there was normal concentration of the dye. Review of the previous x-ray examinations with particular reference to the stomach focussed attention on an area suspicious of intrinsic gastric disease which had not been clearly defined in the routine examination. Special technics of visualization now revealed the presence of two well developed ulcers in the region of the lesser curvature, one in the mid-portion and another nearer the pylorus. At operation the original diagnosis was confirmed. The resected specimen also showed diffuse chronic hyperplastic gastritis with abundant lymphoid infiltration of the mucosa and submucosa. The larger ulcer had penetrated into the body of the pancreas, accounting for the character of the pain and its radiation, which had suggested pancreatitis clinically. The patient did well and was discharged but was readmitted six weeks later because of epigastric pain and vomiting attributed to adhesions with partial obstruction. These symptoms were relieved without operation. She was discharged but continued to suffer with anorexia, periodic nausea and vomiting, and occasional abdominal pain.

A little more than a year later, three months before her death, the patient was hospitalized again in a state of advanced debility and emaciation, weighing 86 pounds, and manifesting air hunger. She was extremely pale and her hemoglobin, which had been 66 per cent three months previously, was now 39 per cent (6.25 gm. per cent), red blood cells 2,030,000 per cu. mm., white blood cells 18,100 per cu. mm., and polymorphonuclears 79 per cent. Occasional nucleated red blood cells were present. Reticulocytes were 4.7 per cent. The tip of the spleen was palpable. The anemia was interpreted as some form of chronic hemolytic anemia. Examination of the bone marrow showed mild erythroid hyperplasia and no other significant findings. The cause of the hemolytic syndrome was not identified. An L.E. test was reported as negative. The serum non-protein nitrogen was 46.5 mg. per cent. The urine concentrated to 1.012 and showed 1-plus albuminuria. Her blood pressure, which had been normal previously, was now slightly elevated, 165/95 mm. Hg. As a supportive measure the patient was given a transfusion. On the following day she was found to be in profound stupor. She moaned on painful stimulation, but was otherwise unresponsive. Her blood pressure was 170/88 mm. Hg. The urine was negative for sugar and acetone. No cause was found for the stupor and it was thought that she might have been oversedated inadvertently. On the following day she was completely alert and cheerful. After more than a week had passed the true cause of the stupor was discovered. In her bed table the nurse discovered a bottle containing two tablets and learned from the patient that two days previously the bottle had contained fifty tablets. After much pressure the husband was prevailed upon to reveal the nature of the tablets. They contained aspirin gr. 3.5, caffeine gr. .50, phenacetin gr. 2.5, and cyclopal (a barbiturate) gr. .75. It subsequently transpired that the patient had been taking these tablets for the previous five and a half years without any physician's knowledge and authorization. At first the patient had



FIG. 1. Uneven contraction of kidney in chronic interstitial nephritis.

consumed about 200 tablets a month, later ten to twenty-five a day. She had sworn her husband to secrecy and became extremely agitated when her secret was made known. After much patient urging and encouragement by her physician she finally agreed to stop taking the tablets. For a while she was restless and depressed but had no true withdrawal symptoms. She continued to complain of her usual headache and lack of desire for food. For a while she had pains in her muscles and an urticarial eruption. X-ray examination of the chest revealed no abnormalities except for demineralization of the ribs and other bony structures, not noted on previous examination. The bony change was held by the radiologist to be caused by bone marrow hyperplasia of a compensatory type or some type of blood dyscrasia. Upon discharge from the hospital her hemoglobin had risen to 62 per cent, and the red blood cell count was 2,730,000 per cu. mm.

Her headaches persisted and re-examination disclosed marked hyperesthesia of the entire body, chiefly in the head, neck and upper extremities. "Trigger points" in the trapezius muscles were discovered and procaine infiltration produced temporary amelioration. Because of anemia, which had persisted in moderate degree, she was given another transfusion. At times she had abdominal cramps, nausea and occasional vomiting.

Two and a half months after discharge from the hospital she was readmitted in a stupor. This had developed gradually over several days. On admission she could not be aroused. She was extremely emaciated and had noisy Kussmaul breathing. Her complexion was described as "somewhat brownish and

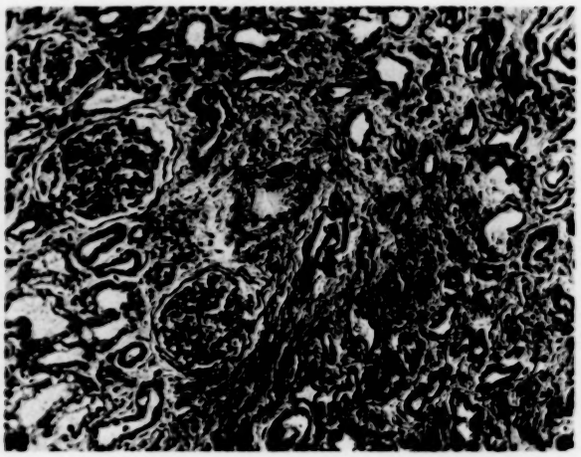


FIG. 2. Tubular loss and advanced scarring in cortex with preservation of glomeruli.

sallow" and there was slight puffiness of the eyelids. Loud moist rales were heard throughout the chest. The hemoglobin was 72 per cent (11.2 gm. per cent), hematocrit 37 per cent. The serum non-protein nitrogen was 140 mg. per cent, CO_2 20 volumes per cent. The clinical picture suggested uremia but the etiology was unclear although the possibility of drug causation was mentioned. The urinary output was markedly reduced and a uremic frost developed on her face. Examination of the urine showed albumin 1-plus, specific gravity 1.010, and occasional white and red blood cells in the sediment. The serum non-protein nitrogen rose to 164 mg. per cent. Her blood pressure ranged between 150/110 and 204/110 mm. Hg. After a brief convulsion she died quite suddenly.

At autopsy, the subject was extremely emaciated. The skin had a pale yellowish brown tinge which was particularly noticeable on the face. No jaundice or edema was seen.

The most interesting findings were in the kidneys, which were somewhat enlarged and had a combined weight of 310 gm. The capsules were fairly tightly adherent and difficult to strip. The exposed surface of each kidney presented a peculiar pebbly unevenness. (Fig. 1.) The elevated portions were somewhat lighter in color than the depressed portions, but there was no sharply defined separation and no obvious scars, cysts or suppuration. The kidneys were cut with much resistance and their cut surface disclosed corresponding uneveness in thickness of the cortex. The corticomedullary junction had a fuzzy indistinctness. The cortex had a light tan coloration. The medulla appeared fleshy and reddish brown in color and its markings were blurred. The tips of several of the pyramids were necrotic and had a muddy brown discoloration.

Microscopically the narrowed regions of the cortex were found to be large indefinitely defined wedge-shaped areas of tubular atrophy and stromal fibrosis. (Fig. 2.) The convoluted tubules which remained

were shrunken and separated by delicately fibrillar collagen infiltrated with scattered lymphocytes and a few neutrophils or eosinophils. In Van Gieson and PAS-stained slides the basement membranes of the affected tubules were thickened into broad wavy hyalin ribbons and contributed a considerable share to the stromal thickening. In areas of less contraction of the cortex the tubular elements were better preserved or entirely normal and stromal thickening was less marked. The loops of Henle and collecting tubules were least affected.

In the intervening areas of cortical expansion the tubules and glomerular spaces were often strikingly widened but the glomerular loops were compressed and bloodless. These findings suggested obstruction with retrograde glomerular tamponade and were correlated with distal blockage by large, coarsely granular casts within the collecting tubules of the medulla.

Early stages of the process were occasionally evident in areas which had not yet undergone much scarring. The initial phase appeared to consist in a degenerative change of the proximal convoluted tubule in the form of granular or foamy swelling and shedding of tubular epithelium into the lumen. The cytoplasm was often impregnated with red cell fragments or minute hemorrhages. In many tubules the epithelial cells contained golden-brown granules which gave a deep blue reaction with the Gomori ferrocyanide-hydrochloric acid stain for iron. Occasional minute cysts were observed; these were lined with tubular epithelium and were distended with granular eosinophilic detritus. A few granulomatous nodules were encountered in which fibroblasts and histiocytes were collected about a center of necrotic tubular epithelium.

The glomeruli were remarkably well preserved even in areas of advanced tubular atrophy and stromal sclerosis. A few were obliterated and hyalinized and others exhibited slight pericapsular and intercapillary hyalin swelling of the basement membrane (PAS stain). The blood vessels were not remarkable except for moderate hypertrophy of the media of small arteries and contraction of arterioles in areas of dense fibrosis.

Sections through necrotic papillae showed simple devitalization of tissue (tissue ghosts) and these were partly or completely demarcated by broad zones of suppuration. Occasional minute burrowing abscesses were encountered in adjacent regions. The cause of papillary necrosis was not evident from study of these sections although the changes were compatible with the effects of ischemia.

The lungs were heavy with congestion and edema and had a gelatinous cut surface. Microscopically the alveoli contained abundant colloid-like proteinaceous exudate which stained rather deeply and was often inspissated in a well defined layer along the walls of alveoli and alveolar ducts as a "hyalin membrane." Areas of early suppurative bronchopneumonia were present in dependent portions of both lungs. The heart exhibited mild hypertrophy of the left ventricle and slight focal interstitial inflammation. The liver was normal in size and contour and of an extraordinary dark russet brown color; microscopically the polygonal cells of the parenchyma contained much golden brown granular pigment which stained deeply for iron in the outer portions of the lobule and faintly in the region of the central vein. The Kupffer cells stained deeply for iron in all parts of the lobule. The spleen was slightly enlarged and firm and exhibited microscopically an abundance of iron-staining pigment within the hyperplastic reticulum cells of the pulp and within numerous large histiocytes collected within the widened congested sinusoids. Similar siderophages were present also in the bone marrow examined in section of the lumbar vertebrae, which was otherwise considerably depleted of normal elements, especially erythrocyte precursors. The bony trabeculae seen in these sections were well formed in number and thickness and showed no appreciable activity of osteoblasts or osteoclasts. On gross examination the brain appeared normal; microscopically much evidence of edema was seen in the form of distended perivascular spaces with tamponade and obliteration of many of the small blood vessels, especially in the cortex. Some of the ganglion cells seemed to contain fine brownish granules in addition to their normal cytoplasmic granules but were otherwise normal, and there were no glial or vascular changes of significance. Sections of skeletal muscle (suboccipital group) showed fading and shrinking of isolated fibers and a few lymphocytes and macrophages in the perimysium. The majority of the fibers appeared normal.

The anatomical diagnoses were advanced sclerosing tubular nephritis with necrotizing papillitis; extensive serous pneumonitis with hyalin membrane formation and early suppurative bronchopneumonia; hypoplasia of bone marrow; hemosiderosis of hepatic and renal parenchyma and cellular reticuloendothelium of liver, spleen and bone marrow; moderate hyperplasia of splenic reticuloendothelium; mild hypertrophy of left ventricle; diffuse edema of brain; slight suboccipital myositis; exteme emaciation; hyperpigmentation of skin; status after previous drainage of peritoneal abscess and subtotal gastrectomy for two gastric ulcerations.

COMMENTS

In the case cited the drug was taken at first in ordinary doses and the dose was increased gradually over a long period of time until, during the last three years of her life, the patient was taking ten to twenty-five tablets daily. From the data available to us it was computed that she had taken well over twenty thousand such tablets in about five and a half years.

This amounted to a total intake of at least 3.5 kg. of phenacetin. The significance of phenacetin abuse was not considered seriously as an explanation for the peculiar sclerosing nephritis found at autopsy until an abstract of Moeschlin's paper appeared shortly afterward in the *J. A. M. A.* [*10*]. A review of Moeschlin's paper [*9*] and of publications cited by him made it clearly evident that the abnormalities found in this patient's kidneys corresponded closely with those described in the Swiss literature beginning with the report of Spühler and Zollinger in 1953 [*6*].

As indicated previously, the renal changes observed in their series were interpreted by them as the result of primary inflammation of the renal stroma followed by scarring and were, therefore, classified as "chronic interstitial nephritis." The gross description of the kidneys in their subjects (and accompanying illustrations) portrayed details which matched those of our patient, for example, the peculiarly uneven surface of the kidneys, the irregular thickness of the cortex revealed on cut section, and the necrosis of the tips of the pyramids. Their microscopic findings were also paralleled by our own, namely, broad areas of interstitial fibrosis of the cortex coupled with loss or degeneration of convoluted tubules and hyalin thickening of the basement membranes. The glomeruli and blood vessels were largely unaffected.

Some of the microscopic features in our case inclined us to consider a somewhat different interpretation of its pathogenesis. For example, there were many areas which appeared entirely normal or nearly so, and many other areas displayed early changes of minor or intermediate degree. Where the process seemed to be in its initial phase the amount and intensity of interstitial inflammation and fibrosis were meager in proportion to the severity of tubular degeneration, which often bordered on necrosis. The basic lesion thus seemed to be multifocal and centered about the convoluted tubules rather than diffused through the stroma. The interstitial changes, however striking and extensive, seemed therefore to be the expression of a stromal reaction to tubular damage.

If one considers the wide variety of toxic agents which can cause tubular injury it is surprising that sclerosing nephritis of this type is seen so infrequently. Evidently simple injury of tubular epithelium cannot in itself account for interstitial inflammation and scar tissue proliferation. Even in the case of extreme tubular injury, such as observed in bichloride of mercury poisoning, there is only a moderate degree of interstitial proliferation during the healing phases. It is unlikely, therefore, that the interstitial changes seen in phenacetin nephritis result merely from destruction or damage of renal tubular epithelium. The presence of iron-staining granules in the epithelium of many of the tubules suggests a partial answer. Many patients with hemoglobinuria of various types, acute or chronic, mild or severe, escape renal injury; even in paroxysmal nocturnal hemoglobinuria, in which the patient excretes hemosiderin continuously and may have "black water" with as much as 20 gm. of hemoglobin excreted in twenty-four hours, there may be little or no impairment of the kidneys [*12*]. On the other hand methemoglobin is more readily precipitated in the renal tubules than is hemoglobin, especially if the urine is acid, and this constitutes a cardinal danger in methemoglobinemia, regardless of the cause [*1*]. In acidotic dogs methemoglobin solutions have been shown to produce renal injury, i.e., hydropic degeneration in proximal convoluted tubules and necrosis in distal convoluted tubules [*11,13*]. Possibly acid hematin and other iron-protein complexes precipitated in an acid milieu continue to exert an irritant influence for long periods of time and so excite proliferation of fibrous tissue. The possibility of hypersensitiveness to phenacetin or its degradation products (or to a drug-tissue antigenic complex) expressing itself in active inflammation about injured tubules, as in sulfonamide nephropathy, must also be considered. Final answers on these and related questions must await the accumulation of much more evidence.

One may properly question the assumption that this patient's assemblage of disorders is ascribable solely to phenacetin. Actually her most distressing symptoms other than headache were the result of gastric irritation and ulcerations which progressed to perforation and formation of a peritoneal abscess, followed by penetration of a gastric ulcer into the pancreas which mimicked the clinical syndrome of acute pancreatitis. It is conceivable that the additive or synergistic action of aspirin and caffeine was in part responsible for gastritis and gastric ulcerations in this patient [*14,15*] and perhaps might also have contributed to her chronic anorexia and profound weight loss (weight at death was 82 pounds). Without doubt other elements enter

the picture when one attempts to interpret these and other symptoms in the full perspective of an exceedingly complex situation. Psychogenic anorexia had been considered seriously in differential diagnosis. Explanation for her weight loss would be incomplete without mention also of the contributory effect of hypermetabolism. In fact hyperthyroidism was strongly suspected because of her extreme nervousness, tremor, slight lid-lag and stare, and a basal metabolic rate of plus 21 per cent. The radioiodine uptake was 30 per cent of the administered dose, which was considered within the normal range, and there was no improvement after administration of propylthiouracil. Drug-induced hypermetabolism remains a possibility. Caffeine is known to exert a distinct stimulating effect on body metabolism even in ordinary doses [*1*]. Aspirin may also have played a part. Thus in recent years information has come to light which indicates that an important part of salicylate action is its action on metabolism, specifically a marked increase in oxygen consumption of skeletal muscle [*16*]. In the series of cases published by Spühler and Zollinger [*6,7*] certain details are reported which suggest the possibility that caffeine and salicylates may have been responsible for parts of the syndrome which cannot be accounted for wholly by chronic phenacetin intoxication. Thus one of their patients died of perforated ulcer and several others were suspected of having gastric cancer because of weight loss and repeated vomiting.

A surprising feature of our case was the relative mildness of anemia, except for an episode late in the clinical course of the disorder when it became severe enough to cause air hunger and prostration. The finding of target cells, microspherocytosis and a reticulocyte count of 4.7 per cent was compatible with the diagnosis of hemolytic anemia. The bone marrow aspirate also showed increased erythropoiesis. No red cell inclusion bodies (Heinz bodies) were demonstrable in routinely prepared blood smears (Wright stain). On her final admission in uremia she had only slight anemia (hemoglobin 72 per cent (11.2 gm.), hematocrit 37 per cent).

In Moeschlin's nine patients, all suffering from renal insufficiency, the hemoglobin levels ranged between 5.5 gm. and 10 gm. per cent (35 to 65 per cent) and red cell counts between 1.8 and 3.0 million per cu. mm. [*9*]. In two of his fatal cases the hemoglobin was 45 and 49 per cent, in one other case it was 57 per cent, and in a fourth 86 per cent. All of his patients had some degree of sulfhemoglobinemia. Evidently the presence of anemia cannot be counted on in guiding clinical suspicion toward the possibility of phenacetin poisoning. When present, as in our own patient, anemia probably reflects the failure of red cell regeneration to keep pace with augmented destruction because of the intervention of additional factors, i.e., intercurrent infection or renal insufficiency.

Inclusion bodies within the red cells, which were considered by Moeschlin to be a characteristic feature of phenacetin poisoning, were found by him in 3 to 14 per cent of the red cells of affected patients. Schaub [*8*], however, reported red cell inclusions in only two of his twenty-four patients, all of whom had some degree of anemia. The disparity in these data may possibly result from differences in technic. Moeschlin stipulated the importance of supravital stains or phase microscopy for the demonstration of inclusion bodies within the red cells, and routine preparations of blood smears are therefore unlikely to provide much aid in diagnosis.

Although cyanosis was never pronounced enough to be clearly recognized in our patient, she had a notably sallow complexion which might have been classed as both "muddy" and "café au lait." In the presence of long-continued headache and nervous irritability this could have awakened suspicion of sulfhemoglobinemia, which might have been quickly confirmed by examination of a sample of blood.

SUMMARY

A 34 year old housewife died in uremia following prolonged excessive use of a proprietary headache mixture. In the course of five and a half years she had taken more than 20,000 capsules of the mixture, comprising an estimated total of at least 3.5 kg. of phenacetin, 5.0 kg. of aspirin and 0.7 kg. of caffeine. Autopsy revealed advanced degenerative changes in the kidneys, resembling the condition described in the recent Swiss medical literature in patients consuming large quantities of phenacetin.

As with many victims of phenacetin habituation, this patient's concealment of her habit defeated all efforts to explain her symptoms during life.

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Severe Hypoglycemia after the Ingestion of a Sulfonylurea Compound*

MARVIN A. SACKNER, M.D. *and* LUCY J. BALIAN, M.D.

Philadelphia, Pennsylvania

SEVERE hypoglycemia is an uncommon reaction to the sulfonylurea compounds [*1–3*]. This report is concerned with a patient in whom permanent damage to the brain secondary to hypoglycemia developed after the ingestion of a new derivative of the sulfonylurea series, chlorpropamide. It is of particular interest because serial electroencephalograms and psychological tests were obtained.

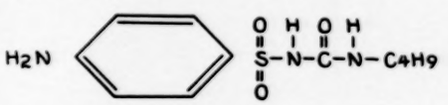
Chlorpropamide (Fig. 1) is a white odorless crystalline compound with a typical taste. It is soluble in alcohol, moderately soluble in chloroform, sparingly soluble in benzene and ether, and insoluble in water. The melting point is 127.2° to 127.6°C. Its concentration in serum can be determined by a spectrophotometric method. The acute oral toxicity in mice and rats is comparable to that of tolbutamide. Long term administration to dogs in dosages of 50 to 200 mg./kg. did not result in any deleterious effects on the blood, liver and kidney. The drug is excreted unchanged by the kidney.

Following the single oral administration of chlorpropamide, a hypoglycemic response persists after forty-eight hours. In man, serum levels reach a plateau within three to five days. In the treatment of diabetic patients, the recommended starting dose is 500 mg. daily, the maintenance dose being adjusted up or down by increments of 100 to 200 mg. at intervals of three to five days [*4*].

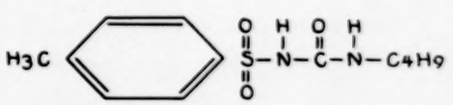
CASE REPORT

C. R., a forty-five year old white man, was admitted in a comatose condition to the Philadelphia General Hospital on April 16, 1958. The patient, one of forty-five volunteers who were taking chlorpropamide (Diabinese®), received 2 gm. of this drug on April 13 and April 14, respectively. About midnight on April 15 he exhibited hypoglycemic symptoms which responded readily to oral administration of carbohydrates. At 6:00 A.M. on April 16 he was found in a comatose condition. He was transferred to the institutional infirmary and treated with intravenous glucose and saline solution; he received a total of 175 gm. of glucose in a twelve-hour period. He remained in a coma and was transferred to our hospital that evening.

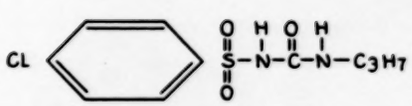
The past medical history was obtained from his institutional records. In 1945 appendectomy, chole-



Carbutamide



Tolbutamide



Chlorpropamide

FIG. 1. Chemical structure of sulfonylurea compounds.

* From the Philadelphia General Hospital, Philadelphia, Pennsylvania. This study was supported in part by Charles Pfizer & Company, Inc., Brooklyn, New York.

TABLE I
LABORATORY FINDINGS

Day	Hemoglobin (gm. %)	White Cell Count (thousand/cu. mm.)	Urine							
			Specific Gravity	Protein	Sugar	White Blood Cells	Red Blood Cells	Casts	Cultures	Twenty-four-Hour Protein
1	....	....	1.008	2 plus	0	4–8	7–10	5–8 finely granular	Sterile	.....
2	13.9	14.7	.....	.....	.....	.....	.....	.....	.....	.....
3	14.4	12.4	.....	.....	.....	.....	.....	.....	.....	.....
4	13.9	14.9	1.007	1 plus	2 plus	15	0	0	Few pseudomonas	.....
6	12.6	9.3	.....	.....	.....	.....	.....	.....	.....	.....
7	....	....	.....	.....	.....	.....	.....	.....	.....	1.3 gm.
9	12.7	10.6	1.015	1 plus	0	2–4	3–4	0	Pseudomonas	.....
11	....	....	.....	.....	.....	.....	.....	.....	.....	1.2 gm.
12*	12.6	9.0	1.015	2 plus	0	30–35	.....	.....	.....	.....
24	13.8	10.2	1.021	1 plus	0	Rare	0	0	.....	.....
50	15.0	8.9	1.017	1 plus	0	1–2	3–4	0	.....	.....

* Day 12 = Phenolsulfonphthalein test: 15 minutes, 5 per cent; 30 minutes, 8 per cent; 45 minutes, 20 per cent; 1 hour, 10 per cent.

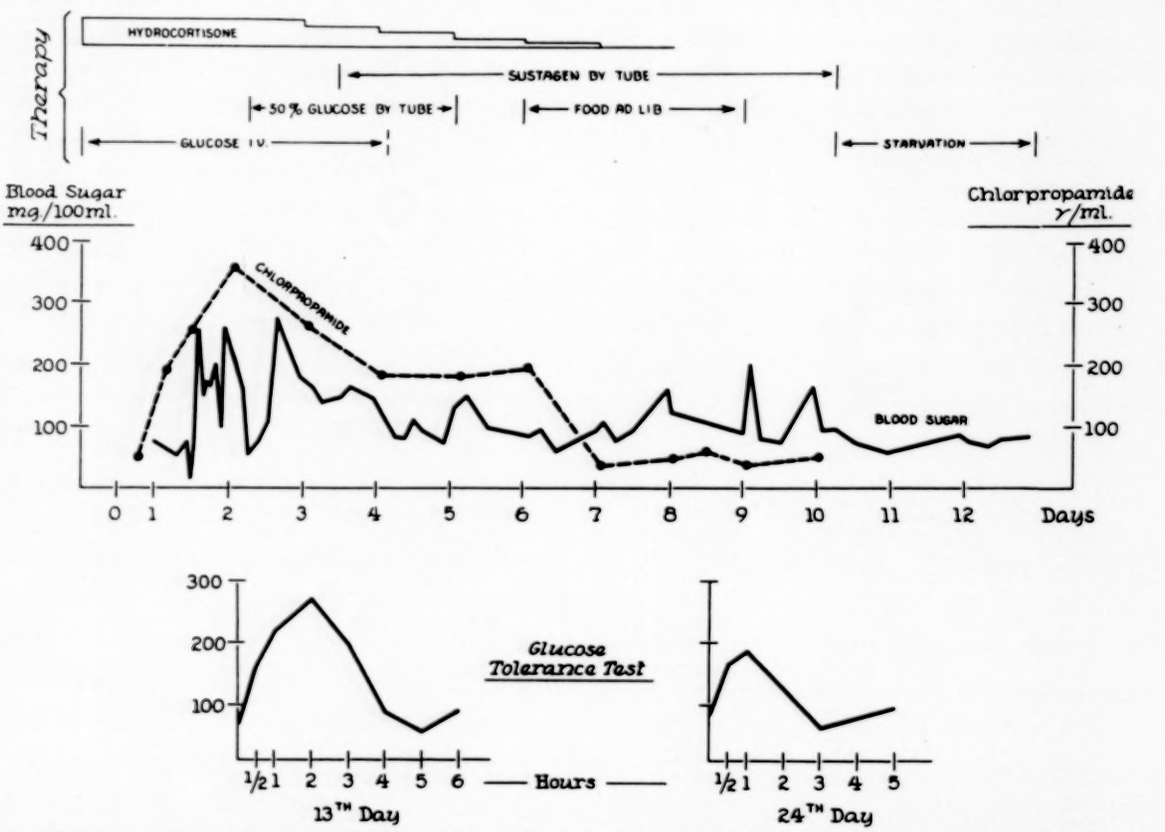


FIG. 2. Blood sugar and chlorpropamide levels. Blood sugars were determined by the Folin-Wu method. Initially the blood sugar levels were low despite constant administration of hypertonic glucose solution intravenously. Although the levels of chlorpropamide remained elevated through the sixth day, normal blood sugar concentrations were present at that time. The blood sugar levels were normal during a seventy-two-hour fast. A glucose tolerance test immediately thereafter resulted in a diabetic curve. Two weeks later, on a normal diet, a normal curve was obtained

cystectomy and drainage of an abscess were performed. He noted jaundice in 1955. In 1956 the urine showed sugar 0, albumin 4 plus, 8 to 10 red cells and 2 red cell casts. The sedimentation rate was 41 mm. Albuminuria was noted also in subsequent urine specimens through 1958. An intravenous urogram in 1956 was normal. In 1956 and 1957 roentgenographic examination of the upper gastrointestinal tract showed a chronically scarred duodenal cap. In January 1958 he had an episode of slight twitching of the mouth and protrusion of the tongue which lasted a few minutes. He did not lose consciousness and this episode was thought to be malingering. An electroencephalogram taken at this time was within normal limits.

Physical examination revealed a comatose, well nourished, white man in decerebrate rigidity. He was in moderate respiratory distress and required frequent aspiration of copious amounts of thick secretions. The temperature was 99.8°F., respirations 34, pulse 54, blood pressure 120/90 mm. Hg. The positive findings were confined to the neurologic system and changed rapidly from moment to moment. He occasionally had generalized tonic movements which lasted a minute or less. The pupils were alternately widely dilated and constricted, and reacted poorly to light. The eyes deviated to the left, and at times were uncoordinated. The corneal reflexes were sluggish. The optic discs were pale, no hemorrhages or exudates were found. The extremities were alternately spastic and flaccid. A coarse generalized tremor was occasionally seen. Bilateral Babinski signs were elicited. Coarse rhonchi were heard in both lung fields. The heart was not enlarged, the rhythm was regular and no murmurs were heard. The abdomen was soft, and the liver and spleen were not palpable.

The therapy and laboratory findings are summarized in Tables I and II, and Figures 2, 3 and 4. It is noteworthy that blood sugars of 77 mg. and 15 mg. and a cerebrospinal fluid sugar of 22 mg./100 ml. were initially recorded despite the simultaneous intravenous infusion of high concentrations of glucose.

The patient's course in the hospital was characterized by a relatively rapid and steady improvement. After three to five hours of treatment he intermittently began to resist movement of his extremities and the Babinski signs disappeared. The following day he occasionally groaned, yawned and sneezed, and only intermittent spasticity of the left arm persisted; however, this disappeared completely by the sixth day. His behavior resembled that of a "thalamic animal" for about a week. An electroencephalogram obtained on the third day showed scattered high voltage abnormal slow waves, 4 to 6 per second, throughout both hemispheres, especially marked in both temporal lobes. (Fig. 5.)

On each subsequent day the patient was able to respond more appropriately. An electroencephalogram obtained on the sixth day showed marked

TABLE II

LIVER STUDIES

Day	Bromsulphalein Retention (% in 45 min.)	Serum Alkaline Phosphatase (Bodansky units)	Serum Bilirubin (mg./100 ml.)	Cephalin flocculation	Thymol Turbidity	Thymol Flocculation	Serum Total Protein (gm./100 ml.)	Protein Electrophoresis					Serum Cholinesterase (Michel units)	Serum Cholesterol (mg./100 ml.)	Serum Cholesterol Esters (%)	Serum Glutamic Oxaloacetic Transaminase	Serum Glutamic Pyruvic Transaminase	Prothrombin Time (%)	Serum Iron (gamma./100 ml.)
								Albumin (gm./100 ml.)	Globulin (gm./100 ml.)										
									Alpha1	Alpha2	Beta	Gamma							
2*	..	1.4	0.6	0	2.4	0	5.5	1.83	0.61	0.87	1.05	1.1	0.46	178	61	21	26	75	..
3	31	...	...	..	...	..	...	....	....	....	....	...	....	...	..	..	..	...	27
6	16	...	...	..	...	..	5.6	....	....	....	....	...	....	...	..	..	..	...	..
10†	..	2.5	...	..	...	..	...	....	....	....	....	...	....	...	..	..	..	100	..
24	12	...	...	0	3.5	17	7.0	2.90	0.49	0.96	1.1	1.6	....	...	..	..	..	...	..
50	14	1.7	0.2	0	2.5	0	7.3	3.41	0.46	0.85	0.9	1.7	0.72	313	70	..	..	...	78

* Day 2 = Urinary amino acids: alanine, aminoacetic acid, cystine, glutamine, lysine hydrochloride, beta-aminoisobutyric acid and taurine were present. There appeared to be an increase in total quantity but no pathologic increase in any individual amino acid.

† Day 10 = Liver biopsy: normal liver tissue.

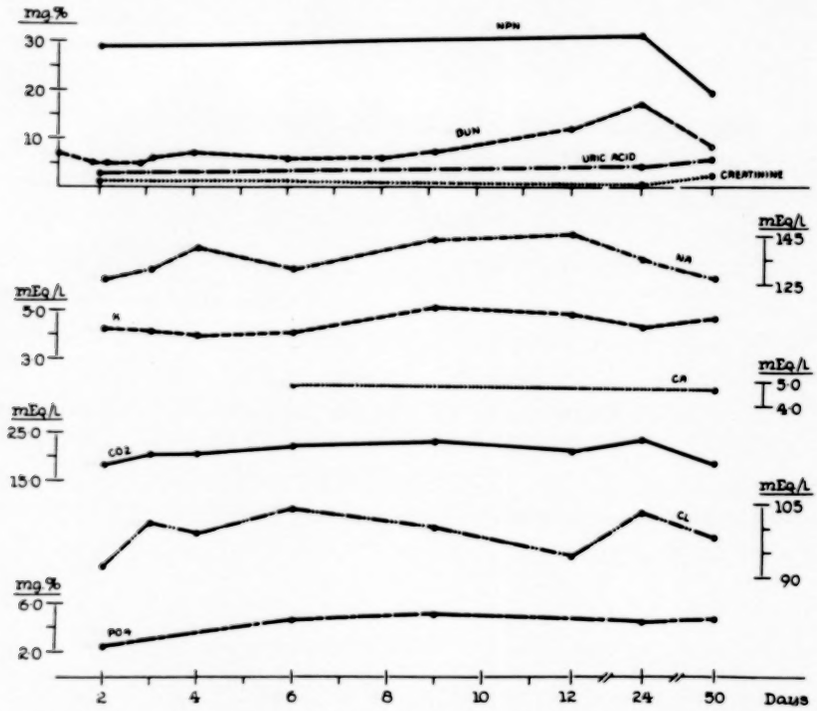


FIG. 3. Blood chemical studies. Throughout most of his hospitalization, the patient had consistently low levels of blood urea nitrogen without an associated decrease in non-protein nitrogen.

improvement, as compared with the previous tracing, although the abnormalities previously mentioned were still present.

A brief psychological examination on the thirteenth day revealed a marked expressive aphasia. A third electroencephalogram taken at that time showed more damage than the previous tracing. There were a moderate number of high voltage abnormal slow waves 3 to 5 per second, throughout both hemispheres, at times occurring in short bursts, the abnormalities again being more marked in both temporal lobes.

The patient was returned to his institution on the fifteenth day. He was able to feed and dress himself with some coaxing and could walk normally. He had complete amnesia for all recent events and his memory for remote events was generally poor.

Further improvement was noted on a fourth electroencephalogram obtained thirty-seven days after the episode of coma. The electroencephalogram showed occasional high voltage slow waves, 3 to 5 per second on the right, while the left hemisphere, particularly the temporal and occipital regions, showed a moderate number of high voltage abnormal slow waves.

Information on the patient's previous personality and intellectual level was obtained through the cooperation of the Department of the Army. His performance on several intelligence tests placed him at an average or low average level. He was examined by Army psychiatrists on several occasions because of criminal behavior but was not considered psychotic. A diagnosis of inadequate personality with alcohol addiction was made.

A number of psychological tests were given to the patient fifty days following the onset of coma. These included the following: (1) Bender visual-motor gestalt, (2) Rorschach, (3) Wechsler memory scale, (4) Eisenson's tests for aphasia, (5) Stanford-Binet vocabulary, (6) Goldstein-Scheerer stick test, cube test and Weigl color form test. The results of these tests may be summarized as follows: (1) Definite evidence of cortical damage of a diffuse nature, as manifested by loss of abstract ability, disorganization of behavior under stress, and marked perseveration; (2) severe damage in the speech areas, i.e., temporal lobes; and (3) intellectual function at moronic level.

COMMENTS

The mode of action of chlorpropamide is similar to that of tolbutamide and carbutamide. These drugs are thought to stimulate endogenous insulin release and potentiate insulin action at a hepatic level. The present evidence indicates that the drugs in question do not increase peripheral glucose utilization [*5*].

The patients reported to have had severe hypoglycemic reactions received the usual

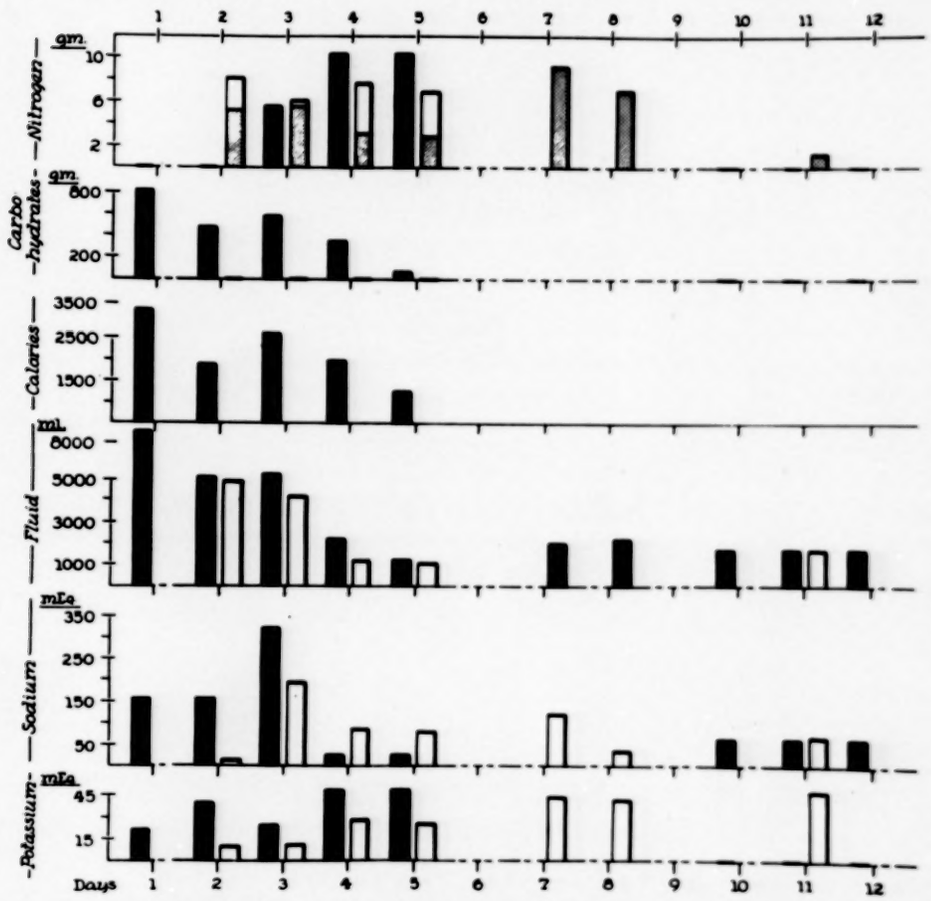


FIG. 4. Partial balance studies. The solid blocks represent intake, clear blocks output, and striped blocks urea nitrogen. Horizontal broken lines depict unmeasured values, short solid lines depict zero values. However, on days two to four, 2 to 6 gm. of glucose were found in the urine (total reducing substance). On days seven, eight and eleven, only the urine urea nitrogen was measured.

therapeutic doses of carbutamide and were mildly diabetic. The coma, weakness and pyramidal signs associated with the hypoglycemia responded to 100 ml. or less of hypertonic glucose solution given intravenously. One patient relapsed the day after the initial treatment, but again responded to glucose therapy. No permanent damage to the brain has been reported [*1,3*].

The coma, pyramidal signs and increased vagal tone which occurred in our patient are consistent with marked hypoglycemia. Despite simultaneous infusion of hypertonic glucose solutions, the blood sugar drawn shortly after admission was 15 mg./100 ml., and a corresponding cerebrospinal fluid sugar was 22 mg./100 ml. Since blood sugar levels below 25 mg./100 ml. as determined by the Folin-Wu method, represent non-glucose reducing substances, glucose was probably absent from the peripheral circulation [*6*]. Because the chlorpropamide levels were not inordinately elevated, as compared to levels obtained in normal subjects, other factors responsible for the severe hypoglycemic response were investigated. Retention of the drug by diseased kidneys, acute hepatic injury, the coexistence of a functioning islet cell tumor and an idiosyncratic reaction were considered.

The past medical history and the previous and present laboratory findings (Table 1) were consistent with the diagnosis of early glomerulonephritis. The drug was, in fact, excreted more slowly in our patient than in other volunteers [*4*]. However, this does not appear to be a major factor in the production of the hypoglycemic reaction because the blood sugar and chlorpropamide levels failed to correlate. (Fig. 2.)

Our patient might have had pre-existing

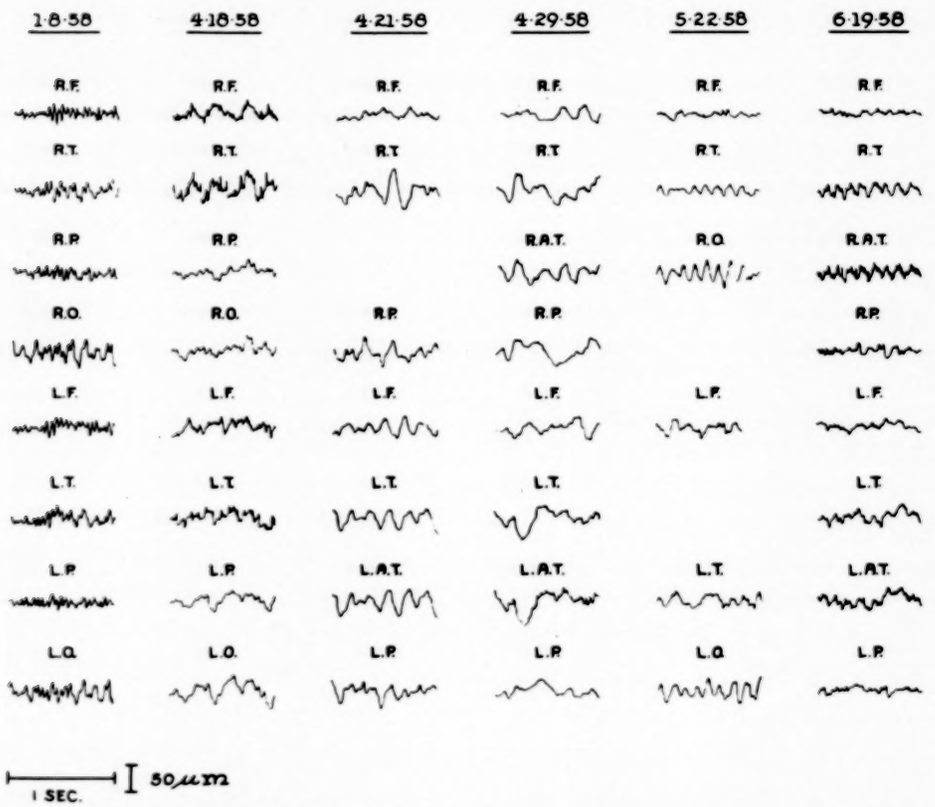


FIG. 5. Serial electroencephalograms. On January 8, 1958, a normal tracing was recorded, four months prior to the hypoglycemic reaction. After the reaction, slow wave activity, most marked in the left temporo-occipital region, was noted.

hepatic disease, in view of the alcoholic history and the episode of jaundice. However, the results of the flocculation tests, serum bilirubin, cholesterol and esters, prothrombin time, transaminases, alkaline phosphatase and biopsy of the liver were normal. (Table II.) The serum iron was low; if hepatic necrosis had occurred, high values would be expected [7]. The results of the bromsulphalein test, serum cholinesterase level and serum protein electrophoretogram were abnormal. The initial retention of bromsulphalein was 31 per cent and subsequent determinations varied from 12 to 16 per cent. This test is said to be the most sensitive indicator of hepatic injury after exposure to hepatotoxic drugs [7]. The serum cholinesterase level of 0.46 Michel units, a value below the low normal value of 0.50 Michel units, is compatible with acute hepatic injury. The serum albumin, which was low, tends to parallel the serum cholinesterase levels [8]. It is noteworthy that high levels of serum cholinesterase were found in schizophrenic patients receiving insulin shock therapy [9]. Pericholangitis may occur rarely with chlorpropamide therapy but has not been associated with severe hypoglycemia [10,11].

The nitrogen balance and urea excretion were within the range expected according to the patient's dietary intake [12]. (Fig. 3.) This is in accord with previous studies which have shown that the sulfonylurea compounds have no effect on nitrogen balance and urea excretion [14,15]. An explanation for the persistently low levels of blood urea nitrogen not associated with a fall in serum non-protein nitrogen or a rise in serum creatinine or uric acid has remained an enigma. (Fig. 4.) An increase in a normal or abnormal non-protein nitrogen compound must have occurred. The most likely possibility would seem to be amino acid nitrogen, since semiquantitative examination of the urinary amino acids showed an increase in total excretion with a normal distribution of the individual amino acids. The latter estimation is the more sensitive indicator of disease [15]. The evidence that chlorpropamide induced hepatic hypoglycemia as a result of

hepatic damage rather than by potentiating insulin at a hepatic level is equivocal, but in view of the patient's clinical course we would favor the latter point of view.

Because of the history of ill defined dizzy spells, the coexistence of a functioning islet cell tumor was suggested. In order to test this hypothesis the patient fasted seventy-two hours to provoke hypoglycemia, which did not occur. (Fig. 2.) The glucose tolerance test immediately upon termination of the starvation period gave a diabetic curve, a normal response after carbohydrate depletion. Two weeks later the test result was normal and random sugar determinations up to the present time also have been normal.

No one explanation for the observed hypoglycemic reaction is possible and it is likely that many factors were operating, an idiosyncratic reaction being presumed to be the underlying cause.

Personality, intellectual and electroencephalographic changes following prolonged hypoglycemic coma have been reported in diabetic patients with overdoses of insulin and in psychotic patients who inadvertently remained in prolonged coma during insulin shock therapy. In the diabetic group, only clinical evidence of intellectual, pyramidal and extrapyramidal deficits have been recorded [*16,17*]. For the most part, such changes in the psychotic group were temporary. A more complete return to normal personality was noted in these patients with the longer periods of coma. In addition, there was diffuse slow wave activity in the electroencephalograms which disappeared in two to six weeks [*18,19,20,21*].

To our knowledge, no cases of hypoglycemic coma have been studied by means of serial psychometric and electroencephalographic technics in non-diabetic and non-psychotic persons. In comparing our patient's performance before and after coma, it is obvious that he suffered severe and extensive damage to the brain leading to marked intellectual deficit. His precoma personality adjustment was that of an aggressive sociopathic individual. He presently functions at the level of a moron and is quite docile, withdrawn and retiring.

A review of the literature revealed no specific electroencephalographic changes following hypoglycemic coma [*18,21*]. In our case, the changes were most pronounced in the left temporal lobe, the dominant side.

SUMMARY

A case of prolonged hypoglycemia following ingestion of a sulfonylurea compound, chlorpropamide, is reported. Marked personality, intellectual and electroencephalographic changes occurred.

Acknowledgment: We are indebted to Dr. Anthony Sindoni, Chief, Metabolic Service, who allowed us to report this case. Dr. Dorothy Macy, Assistant Chief, and Drs. Lester Tarr, Lowell Sparks and John Hart, Medical Residents, assisted in the management of this case. Dr. Aaron Mallin interpreted the electroencephalograms. Serum chlorpropamide levels were obtained through the courtesy of Dr. Domenic Iezzoni.

ADDENDUM

Follow-up psychological studies were made at the Norristown State Hospital six months after the initial hypoglycemic episode by M. Powell Lawton, PH.D. Tests of intelligence indicated some improvement in the patient's level from moronic to the borderline range. Retest three months later, however, with an alternate form of the test showed no further improvement. Although the Rorschach responses on admission to the State Hospital were more suggestive of a schizophrenic psychosis, later results showed striking changes more similar to those seen in the patient with typical organic brain damage.

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Rupture of an Intrahepatic Aneurysm Due to Polyarteritis Nodosa*

EPHRAIM GLASSMAN, M.D.† *and* PHILIP V. SKERRETT, M.D.
Philadelphia, Pennsylvania

THE presenting clinical features of polyarteritis nodosa vary widely, depending upon the distribution of the lesions, and may mimic many other disease states. Specific signs and symptoms may localize the involved areas fairly precisely. In the case to be discussed, the rupture of an intrahepatic aneurysm with the development of a massive hemoperitoneum was the major manifestation of polyarteritis nodosa. This was marked by the onset of signs and symptoms indicating an acute surgical emergency. Preoperative diagnoses included perforated peptic ulcer, acute appendicitis and retroperitoneal hemorrhage. As in many other cases of polyarteritis, attention was diverted from the true diagnosis by the mode of onset.

CASE REPORT

(S. J. No. 27683), a fifty-six year old Negro man was admitted to the U. S. Veterans Administration Hospital, Philadelphia, Pennsylvania on April 30, 1958, for the second time. He complained of bloody, painless urination which had been present intermittently during the preceding month. For two years he had been troubled by occasional headaches which had become persistent and severe during the month preceding hospitalization. He had also noted moderately severe pain in the left "kidney" area of the back for two weeks.

The patient's previous hospitalization was in September 1955 when he was admitted because of weight loss, cough and tarry stools. Studies during that period revealed an atypical pneumonitis which resolved slowly, a duodenal ulcer and mild hypertension in the range of 160/90 mm. Hg. The remainder of the past history and review of systems was non-contributory.

Physical examination revealed a middle-aged, chronically ill Negro. His blood pressure was 210/140 mm. Hg; pulse, 100 per minute; temperature, 98.6°F. The patient was moderately confused and mentally retarded. No venous distention was visible. Examination of the fundi disclosed slight blurring and congestion of the discs and scattered hemorrhages and exudates. The breath sounds were bronchovesicular and diminished in intensity at the right base posteriorly. Coarse rhonchi were diffusely audible bilaterally. The cardiac rhythm was regular. The second aortic sound was accentuated, and a moderately loud, low pitched, rough, early systolic murmur, without transmission, was present at the apex. No abdominal organs, masses or tenderness were palpated. The right testis was tender and small. Slight left costovertebral angle tenderness was elicited. The peripheral pulses were palpable in all extremities and no unusual thickening or beading of the vessels was noted. The remainder of the physical examination was within normal limits.

Laboratory studies at the time of admission revealed a normal hemogram, blood urea nitrogen, creatinine, serological tests, calcium, phosphorus, albumin, globulin, sodium and potassium. The serum chlorides were 88 mEq./L.; serum carbon dioxide content, 35.4 mEq./L. Examination of the urine disclosed a specific gravity of 1.009, 4-plus proteinuria, and innumerable red blood cells. Several urine cultures were sterile. Lumbar puncture revealed a pressure of 330 mm. of cerebrospinal fluid, with 4 white blood cells/cu. mm. and normal values for sugar, protein and chlorides. Bromsulphalein retention was 10 per cent at forty-five minutes using 5 mg. of dye per kg. of body weight. The serum bilirubin was 0.6 mg. per cent. The electrocardiogram revealed a normal sinus rhythm. The R waves were tall in V_3, V_4 and V_5, and the T waves were inverted in I, II, aVL, V_4 and V_6. Roentgenogram of the chest revealed normal-appearing heart and lungs. An intravenous urogram showed prompt, bilateral opacification of the pelvocalyceal system; details were insufficient for evaluation of the calyceal system, but the ureters appeared to be normal. A roentgenogram of the upper gastrointestinal tract demonstrated an ulcer crater on the greater duodenal curvature, measuring 1½ cm. in diameter.

After several days of bed rest the patient's mental status improved considerably. However, his blood

* From the Departments of Medicine and Pathology, Veterans Administration Hospital, Philadelphia, Pennsylvania.
† Present address: Johns Hopkins Hospital, Baltimore, Maryland.



FIG. 1. A cross section of the liver showing hemorrhage into the left lobe; fibrosis, nodules and aneurysms in branches of the hepatic artery.

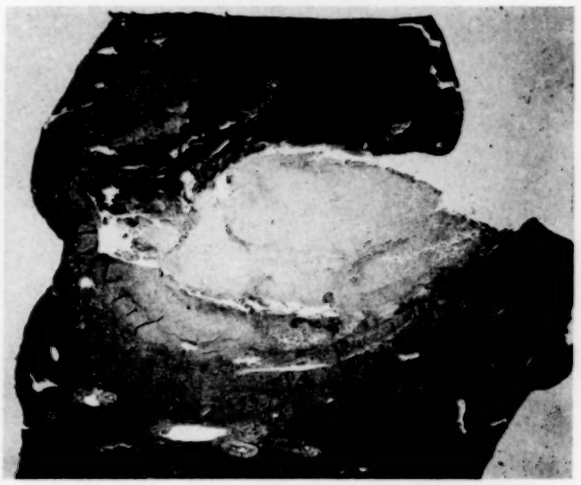


FIG. 2. Liver. Infarction and hemorrhage.



FIG. 3. Gallbladder. Aneurysms of cystic artery and chronic cholecystitis.

pressure remained in the range of 250/100 mm. Hg and he continued to have intermittent hematuria. Frequent paroxysms of hiccoughs were relieved by small doses of chlorpromazine.

On May 29, 1958, after approximately four weeks of bed rest, the patient was awakened by intense, generalized abdominal pain which was most severe in the right lower quadrant of the abdomen and left paraumbilical area. Examination disclosed marked guarding of the entire right side of the abdomen, tenderness to palpation and rebound tenderness in the right lower quadrant. Bowel sounds were absent. His blood pressure fell to 140/128 mm. Hg. A blood count revealed a hemoglobin of 7.6 gm./100 ml., a hematocrit of 28 per cent and a white blood cell count of 28,000/cu. mm. with a marked shift to the left. Roentgenographic examination revealed no apparent evidence of visceral perforation or intestinal obstruction.

Laparotomy was performed on May 29, 1958. The peritoneal cavity contained 2,000 ml. of liquid and clotted blood which was issuing from an irregular tear, 5 cm. in length, in the anterior edge of the left lobe of the liver. The entire left lobe appeared blue and swollen. The tear was oversewn and the peritoneal cavity was thoroughly irrigated and explored. No other source of bleeding was found. The postoperative course was complicated by oliguria and two episodes of grand mal seizures. In spite of blood replacement, parenteral fluids, antibiotics and oxygen therapy the patient died on June 2, 1958.

At autopsy the abdominal cavity contained 3,000 ml. of fluid and clotted blood. The left lobe of the liver was obscured by clotted blood, much of which was subcapsular (Fig. 1), and there was a large retroperitoneal hematoma extending from the pancreas to the pelvis. The heart weighed 450 gm. and showed predominantly left ventricular hypertrophy. The coronary arteries were atherosclerotic and stenotic. The lungs showed minimal degrees of congestion and emphysematous changes at the apices. The lower third of the esophagus was thickened and indurated. A postpyloric chronic ulcer 1.5 by 1 cm. by 0.5 cm. was present. The left lobe of the liver was raised by a subcapsular hematoma and its anterior border was retained by recent surgical sutures. The cut surface of the liver showed a large hematoma measuring 8 by 3 by 3 cm. continuous with the subcapsular hematoma and replacing most of the left lobe. In addition there were numerous small hepatic infarcts. Branches of medium and small hepatic



FIG. 4. Kidney. Aneurysm in arcuate artery typical of those in other organs.

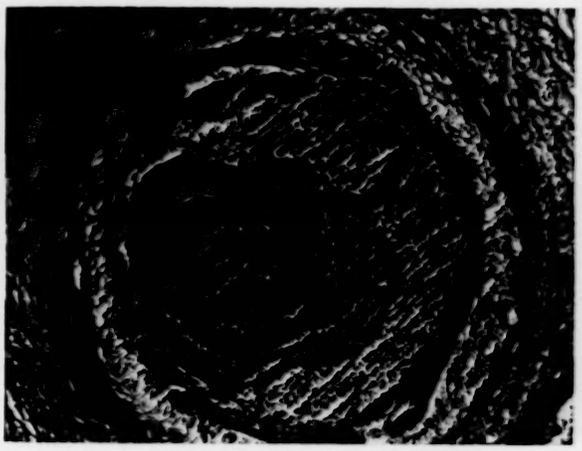


FIG. 5. Left spermatic artery. The typical acute exudative lesion of polyarteritis.

arteries were markedly thickened and showed numerous nodules and small saccular aneurysms at irregular intervals. (Figs. 1 and 2.) The gallbladder was thickened and fibrotic. The branches of the cystic artery stood out as thick prominent cords interrupted at irregular intervals by saccular aneurysms varying in diameter from 0.5 to 1.0 cm. (Fig. 3.) The kidneys showed scattered saccular aneurysms of the arcuate and interlobular arteries. (Fig. 4.) There were corresponding recent small infarcts. The renal parenchyma showed advanced nephrosclerotic changes. The left spermatic artery was sclerotic and nodular. (Fig. 5.) Proximally, it was lost in the retroperitoneal hematoma. The left testicle was enlarged due to marked fibrous thickening of the tunica albuginea. The right testicle was atrophic. The pancreatic artery was markedly thickened and presented nodules and saccular aneurysms along its course. The mesenteric arteries were thickened and sclerotic and showed several small saccular aneurysms (1 to 3 mm. in diameter). The aorta showed a grade IV atheromatosis.

Microscopic examination revealed that the tissues from the involved organs manifested the vascular lesions of polyarteritis nodosa in its different stages of development from (1) acute fibrinoid and mucoid degeneration, (2) leukocytic infiltration, (3) fibroblastic and granulation tissue formation with development of nodules and aneurysms, or thrombosis, and (4) end-stage dense fibrous healing with disappearance of inflammatory cells. The liver, pancreas and kidneys exhibited small recent infarcts with associated arterial thrombosis and saccular aneurysms. The kidneys were the site of severe arterio- and arteriolar sclerosis.

COMMENTS

Involvement of the hepatic arteries by polyarteritis was noted in 42 per cent of 230 cases reviewed by Mowrey and Lundberg [*1*] in 1954 and in approximately two-thirds of the cases cited by Popper and Schaffner [*2*]. The characteristic hepatic lesion is an area of ischemic necrosis resulting from interference with the arterial blood supply.

A review of the literature discloses only five cases in which an intrahepatic hematoma was the major manifestation of polyarteritis. Teacher and Jack [*4*] reported the case of a forty year old white man who was suffering from advanced cardiorenal disease. He died suddenly as the result of intraperitoneal hemorrhage. The autopsy findings were very similar to the subject of the present report. Klotz [*3*] presented the case of a thirty year old white woman who was being treated for a presumptive acute cholecystitis. She died suddenly, and at autopsy a large hematoma was found in the right lobe of the liver, with subcapsular extension and intraperitoneal rupture. The microscopic findings were consistent with polyarteritis nodosa. Aneurysm formation was noted in the intrahepatic arteries. Similar cases were reported by Chitwood [*5*], Solomon et al. [*6*] and Wuktich [*7*]. In each case the presenting signs and symptoms were those of an acute abdominal emergency. In no instance was the diagnosis established prior to exploration or autopsy.

SUMMARY AND CONCLUSIONS

1. A case of polyarteritis nodosa with terminal rupture of the liver due to an intrahepatic hematoma is presented.

2. Five additional cases collected from the literature are reported.

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Idiopathic Hypoparathyroidism Presenting with Seizures*

A Patient Exhibiting Mobilization of Lead During Treatment

ALAN F. HOFMANN, M.D.† *and* J. DONALD SMILEY, M.D.
New York, New York

THIS report concerns the occurrence of pathologically elevated blood and urine lead levels in a patient with idiopathic hypoparathyroidism during treatment with dihydrotachysterol and calcium gluconate. The observation seems worthy of documentation since mobilization of lead during treatment of the hypoparathyroid patient has not been previously reported.

CASE REPORT

A forty-six year old German-born waitress was admitted to the Neurological Institute of the Columbia-Presbyterian Medical Center on June 15, 1956, with the chief complaint of frequent seizures and loss of memory over a two-year period. She had been in excellent health prior to that time.

The past medical, family and social history was noncontributory. The patient's seizures occurred suddenly and without aura. She would lose consciousness for an hour, following which there were several hours of confusion and loss of memory. She had had such an episode, with clonic movements of the entire body, tongue biting and urinary incontinence, about every three months. Dilantin® and phenobarbital therapy were employed without benefit. Three months prior to admission her seizures increased in frequency to once or twice weekly, and she noted blurring of vision and general weakness.

On admission, she was a pale, white woman with no evidence of weight loss. The quality and distribution of hair, the texture of the skin and the state of her finger nails were normal. She was cooperative but unable to give a completely reliable history because of recent and past memory deficits. Her general affect was flattened, and she was quite depressed.

Her temperature was 99°F. and the pulse 72. The blood pressure was 100/60 mm. Hg. The visual acuity was 20/100 in the right eye and 20/70 in the left, with bilaterally enlarged blind spots on visual field survey. Funduscopic examination showed 2 diopters of papilledema bilaterally, with distended retinal veins, normal arteries and several hemorrhages near the disks. (Fig. 1.) The lungs were clear to percussion and auscultation. The heart was not enlarged by percussion, the rhythm was regular, and there were no murmurs. The abdomen was soft and non-tender; no organs or masses were palpated.

On neurological examination, cranial nerve function was intact except for impaired olfactory discrimination bilaterally. On the entire right side of the body there was slight weakness, hyperreflexia and impaired proprioception. The remainder of the physical examination was within normal limits.

The initial clinical impression was a left frontoparietal neoplasm.

Analysis of the urine revealed 1-plus proteinuria and on microscopic examination there were 25 to 30

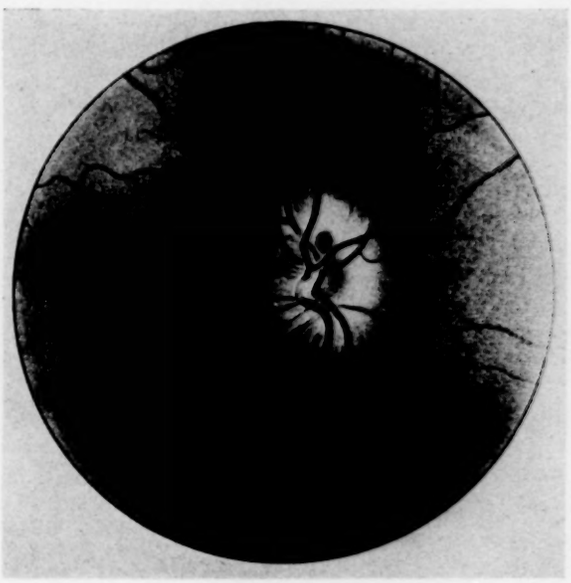


FIG. 1.

* From the Department of Medicine, College of Physicians and Surgeons of Columbia University and the Presbyterian Hospital, New York, New York.
† Present address: National Heart Institute, U. S. P. H. S., Bethesda, Maryland.

white blood cells, 1 or 2 casts, and no red blood cells per high power field. On culture, Escherichia coli was obtained. Examination of the blood revealed a hematocrit of 41 per cent, and an erythrocyte sedimentation rate of 68 mm./hour (Westergren). The white blood cell count was 7,600/cu. mm. with a normal differential. The serological reaction for syphilis was negative.

Further study revealed a serum non-protein nitrogen of 23 mg. per cent and a fasting blood sugar of 90 mg. per cent. The serum alkaline phosphatase activity was 11 to 14 Bodansky units on repeated determinations. Results of the cephalin flocculation test and thymol turbidity test were normal. The serum total protein was 7.2 gm. per cent, with albumin 4.8 and globulin 2.4 gm. per cent. The serum sodium, potassium, chloride and total carbon dioxide levels were all within normal limits. A bromsulphalein test revealed normal dye excretion. The only electrocardiographic abnormality was a prolonged Q-T interval of 0.39 seconds.

Skeletal roentgenograms were within normal limits. The chest roentgenogram, cholecystogram and barium enema showed no abnormalities. An intravenous pyelogram demonstrated minimal right calyceal dilatation, but otherwise the renal architecture was normal. An electroencephalogram was diffusely abnormal, with left frontotemporal slow wave preponderance.

The patient became progressively more obtunded although she experienced no seizures in the hospital. Right and left common carotid arteriograms were within normal limits. A bilateral ventriculogram was performed with normal findings. The cerebrospinal fluid was found to have a normal pressure with a protein concentration of 61 mg. per cent and a sugar concentration of 73 mg. per cent. On microscopic examination there were 15 white blood cells and 4,300 red blood cells/cu. mm.

At this time the diagnosis of lead encephalopathy was suggested to explain the patient's unusual findings. A blood smear for stippling was negative. However, before blood and urine samples could be sent for lead determinations a markedly elevated serum phosphorus level of 7.4 mg. per cent was found, in association with a serum calcium concentration of 5.5 mg. per cent. When these determinations were repeated the phosphorus was found to be 7 mg. per cent, and the calcium 4.2 mg. per cent. With these findings, the diagnosis of hypoparathyroidism was made. The patient was given a low phosphorus diet, and a daily regimen of 3.75 mg. dihydrotachysterol orally and 10 ml. of 10 per cent calcium gluconate intravenously.

Pursuant to the previously considered diagnosis of lead encephalopathy, blood and urine lead determinations were obtained after six days of therapy, with the following results (sample of July 31, 1956): blood lead: 2.5×10^{-2} mEq./L. (0.26 mg. per cent); urine lead: 0.29×10^{-2} mEq./L. (0.30 mg./L.) [*1*]. The upper limits of normal for blood lead are 0.07 to 0.12 mg. per cent [*2*], and for urine lead, 0.08 mg./twenty-four hours [*3*].

For the next three weeks the patient received 3.75 to 7.5 mg. of dihydrotachysterol and 7 to 10 gm. of calcium lactate orally daily. Vitamin D at a daily dose of 100,000 to 200,000 units was then substituted for the dihydrotachysterol, with maintenance on the supplemental calcium lactate. Four weeks after the initiation of therapy the blood and urine samples showed no detectable lead. Smears of peripheral blood for stippling remained negative and random urine testing disclosed no coproporphyrin III.

On this regimen, the patient exhibited marked and continued improvement. Her memory deficit cleared, and her personality reverted to normal. Her fundal hemorrhages faded, the papilledema regressed, and her visual acuity improved to 20/30 in both eyes. The serum calcium and phosphorus concentrations returned to normal levels, and the serum alkaline phosphatase activity dropped progressively to less than 4 Bodansky units.

Since her discharge on July 27, 1956, the patient has remained in good health except for one episode of hypercalcemic headaches and vomiting due to excessive intake of vitamin D. She is well maintained on 100,000 units of vitamin D three times weekly and 12 gm. of calcium lactate daily. A blood lead determination on June 20, 1958, two years after her admission, again showed no detectable lead. Her erythrocyte sedimentation rate, however, has remained elevated, and the electroencephalogram has continued to be diffusely abnormal.

COMMENTS

This patient falls into the interesting group of middle-aged women with idiopathic hypoparathyroidism presenting as a convulsive disorder, with papilledema and other manifestations simulating brain tumor. The diagnosis of idiopathic hypoparathyroidism was finally established by the finding of extremely low serum calcium and elevated serum phosphorus levels. The patient gave no history of previous neck surgery. There were no physical stigmas of pseudohypoparathyroidism and, although her response to exogenous parathormone was not tested, she was assumed to represent a failure of parathyroid hormone synthesis rather than failure of end organ response. Studies are planned to attempt detection of an antiparathyroid hormone antibody or inactivating substance in view of recently reported cases of idiopathic adrenal and parathyroid hypofunction in which these substances were demonstrated in the serum [*4,5*].

Increased serum alkaline phosphatase activity is quite uncommon in hypoparathyroidism, but has been previously reported [*6–8*]. The basis for this is unknown. Results of this patient's liver function studies were entirely normal, and it is probable that the increase in serum alkaline phosphatase activity was of osteoblastic origin. The possibility that the elevated blood lead levels contributed to increased phosphatase activity cannot be excluded; we have been unable to find any reports of patients with lead intoxication whose serum alkaline phosphatase activity was followed. However, results of other liver function tests remained normal in one reported series [*9*]. In animals acutely poisoned with lead there is a marked increase in the alkaline phosphatase of the liver cells as demonstrated histochemically [*10*], but in these experiments the serum enzyme levels were not followed.

The retinal findings of this patient have been reported in other cases of hypoparathyroidism [*11,12*], with as yet little knowledge of their pathogenesis. This appears to be the first case of hypoparathyroidism in which retinal hemorrhages have been present.

The metabolic interrelations between lead and calcium have been the subject of investigation for many years. Gusserow [*13*] in 1861 emphasized the similarity between lead and calcium storage in the skeleton and suggested that changes in the metabolism of the organism as a whole might similarly affect the distribution of lead and calcium between bone and blood. Since that time numerous studies have confirmed the comparable biological behavior of lead and calcium. Vitamin D and dihydrotachysterol increase the absorption of both lead and calcium from the intestinal tract [*14,15*]. The mobilization of bone calcium in animals by administering massive doses of vitamin D has been clearly shown by Hess [*16*] and Ham [*17*]. Albright's work in man [*15*] demonstrated that despite increased intestinal absorption, a negative calcium balance occurs in persons given large doses of vitamin D. It is now clearly established that parathormone increases the rate of resorption of skeletal calcium [*18*]. The studies of Hunter and Aub in man [*19*] and Flinn in animals [*20*] gave confirmatory evidence of skeletal lead mobilization in plumbism by large amounts of parathormone and vitamin D, respectively.

The studies of Sobel [*21*], however, have shown that calcium and lead do not invariably behave identically in the rat; rather, that with appropriate experimental conditions, calcium and lead may be shown to move in opposite directions with respect to bone. It has been suggested that blood lead levels are influenced significantly by serum phosphorus levels, generally varying inversely as the serum phosphorus levels [*22*].

A few studies [*23–33*] have been made on the distribution of lead between red cells and serum, the concentration of ionized lead, and the binding of lead by serum proteins, but the exact distribution of circulating lead is not fully known.

The classical studies of Aub [*26*] and Kehoe [*27*] clarified the normal dietary intake and the steady state of lead absorption and excretion in man. Tompsett's postmortem studies [*28*] demonstrated measurable tissue lead concentrations in man without a history of lead exposure. Kehoe's observations on a small group of persons with a large lead exposure suggest that there is a continuously increased lead excretion after exposure until normal blood and urine (and presumably total body) lead levels are reached [*3*]. However, prolonged osseous storage of lead with a period of normal blood and urine levels may be possible as demonstrated in cats by Aub et al. [*29*] and suggested by other investigators [*30,31*].

The elevated blood and urine lead levels in our patient represented mobilization of lead from bone, since they coincided with the administration of dihydrotachysterol and calcium while the patient was on a constant low phosphorus diet, and the blood lead level fell while she was on the same diet and therapy. Despite repeated efforts, we have been unable to obtain a history of increased lead exposure in this patient.

Recently, reports from Australia have implicated lead as a cause of idiopathic chronic nephritis. These data bear on the question of increased skeletal lead content without increased urinary lead excretion. Henderson [*32*] has found high bone lead concentrations as a result of lead exposure in patients with idiopathic nephritis in Queensland. He cites data from other workers showing normal urinary lead excretion in Queensland patients with all types of nephritis. As these measurements were not made on identical patients, the data are presumptive but not conclusive as to the origin of increased lead stores without concomitantly increased lead excretion values.

Whether mobilization of lead from normal skeletal stores under the influence of vitamin D or parathormone can occur sufficiently rapidly to raise the blood and urine concentration to abnormally high levels has not been determined. Striking lead mobilization does occur in normal persons after one intravenous dose of monocalcium disodium ethylene diamine tetraacetate [*34*].

The fall in this patient's serum phosphorus at the time of the high serum lead level was probably attributable to the phosphaturic effect of dihydrotachysterol in the hypoparathyroid patient [*15*]. Although a fall in serum phosphorus has been noted in a few patients with hypoparathyroidism after calcium infusion [*7,35*], the response of most normal and hypoparathyroid patients to calcium infusion has been a distinct rise in serum phosphorus [*35,36*].

Large doses of vitamin D cause hypercalcemia without significant disturbances of the serum phosphorus levels in normal persons [*37*]. Dihydrotachysterol is now believed to have effects on calcium and phosphorus metabolism quite similar to those of vitamin D [*38*]. It is probable therefore that dihydrotachysterol can mobilize bone lead without changes in serum phosphorus concentrations, although this specific question has not been studied. There were thus two reasons for a shift of lead from bone to blood in this patient: first, dihydrotachysterol probably causes lead mobilization unrelated to changes in serum phosphorus concentrations; second, a falling serum phosphorus level results in a shift of lead from bone to the extracellular phase.

A direct effect of lead poisoning on the morphology or function of the parathyroids has not been clearly demonstrated. No mention is made in the clinical literature of subsequent parathyroid dysfunction after chronic lead poisoning in man. Peisachowitz [*39*] produced both acute and chronic lead poisoning in dogs and cats, and observed hyperemia of the parathyroids without other histologic changes, but he did not follow serum calcium and phosphorus levels. Rutishauser [*40*] produced severe chronic lead poisoning in dogs, to the point of marked emaciation, and noted advanced parathyroid hyperplasia with osteitis fibrosa at postmortem. Renal function was not assessed, and his findings may well have represented secondary parathyroid hyperplasia because of phosphate retention in renal insufficiency.

SUMMARY

A case of idiopathic hypoparathyroidism with a history of repeated grand mal seizures is reported. The patient exhibited papilledema and retinal hemorrhages despite normal cerebrospinal fluid pressure. The fundal findings, unilateral neurological signs and electroencephalographic abnormalities simulated a brain tumor, but cleared after treatment with dihydrotachysterol and calcium gluconate. Lead mobilization from skeletal stores occurred during therapy, and mechanisms involved in interrelationships between lead, calcium and phosphorus metabolism are discussed.

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Coexistent Addison's Disease and North American Blastomycosis*

ROBERT G. FISH, M.D., TIMOTHY TAKARO, M.D. *and* MARTHA LOVELL, M.D.†
Oteen, North Carolina

NORTH American blastomycosis, a chronic granulomatous disease caused by Blastomyces dermatitidis, is characterized clinically by either cutaneous or systemic manifestations. Clinicopathologic studies [*1–3*] indicate that both forms of the disease, with the exception of the direct inoculation type of cutaneous blastomycosis, follow a primary pulmonary infection. In addition to the lungs and the skin, the genitourinary system, the central nervous system, the skeletal system and other organs may be involved. It is not generally appreciated, however, that the adrenal glands may be affected in a significant number of instances.

In the autopsy series of Martin and Smith [*4*], and of Schwarz and Baum [*1*], totaling sixty cases, adrenal involvement was noted in six cases (10 per cent). In an additional review of approximately forty autopsy reports, three more cases were found [*2,5,6*]. It is probable that if all adrenal glands had been searched specifically for the organisms of B. dermatitidis with special stains (periodic acid-Schiff stain, silver methenamine stain) an incidence higher than 10 per cent would have been found.

There has been one previous report of Addison's disease in a patient with proved North American blastomycosis. This patient, first documented by Jacobsen and Dockerty [*5*], with a follow-up note by Kunkel and his associates [*2*], underwent excisional surgery for blastomycotic involvement of the epididymis. Eleven and a half years after the diagnosis was established he was still alive but Addison's disease had developed, presumably due to blastomycosis. In nearly all of the nine autopsy cases of systemic blastomycosis with adrenal involvement which have been reported in the literature there was involvement of some portion of the genitourinary tract as well, and lesions were scattered diffusely in other systems, including the central nervous system, liver, spleen and other organs.

CASE REPORT

R. T.,‡ a fifty-four year old white man, was admitted to the urological service of this hospital November 20, 1951, with a three-week history of perineal pain and symptoms of vesical neck obstruction. The significant physical findings were confined to a tender, firm, enlarged prostate gland and low grade fever. The blood pressure was 110/60 mm. Hg. Roentgenographic and physical examination of the chest were within normal limits except for a few strands of infiltration in the left infraclavicular region. There were no cutaneous lesions. An abundant greenish yellow prostatic secretion was obtained following prostatic massage. The total white blood cell count was 19,900 per cu. mm. with the following differential: neutrophils 85 per cent, lymphocytes 14 per cent, eosinophils 1 per cent. Approximately three weeks after admission, and concurrent with twice weekly prostatic massage and administration of Gantrisin,® 1 gm. every six hours, generalized, sparsely scattered crusted pustular skin lesions developed in the patient. Five weeks after admission a persistent non-productive cough developed. On December 27, 1951, incision and drainage of a large fluctuant prostatic abscess was performed through a perineal approach. Smears and cultures of the prostatic pus produced Blastomyces dermatitidis as did subsequent scrapings and cultures from the skin lesions. Skin sensitivity with autogenous and stock vaccine was negative. A complement fixation test was positive 1:4. Repeat roentgenogram of the chest on January 3, 1952, revealed a diffuse fine mottling or nodularity throughout the entire left lung and the upper two-thirds of the right lung field. During the following five months various forms of therapy were employed including iodides, undecylenic acid,

‡ The genitourinary complications occurring in this patient to November 1953 have been previously reported by Burr, A. H. and Huffines, T. R. in a paper entitled Blastomycosis of the prostate with miliary dissemination treated by stilbamidine. *J. Urol.*, 71: 464–468, 1954.

* From the Veterans Administration Hospital, Oteen, North Carolina.
† Present address: Veterans Administration Hospital, Atlanta, Georgia.

Aureomycin® and sulfonamides. The clinical course during this period was one of progressive deterioration with daily fever, persistent cough, skin lesions, marked weakness, anorexia and occasional nausea and vomiting. The patient also had bilateral epididymitis and repeated recurrences of the prostatic abscess, eventually requiring open drainage. For a period of time the patient manifested disorientation and a left hemiparesis. The spinal fluid contained 102 mg. per cent of protein without an increase in cell content. Although blastomycosis involving the central nervous system was suspected, the organisms of B. dermatitidis could not be recovered from the spinal fluid. Material obtained from the skin lesions and the prostatic secretions were however repeatedly positive on culture for Blastomyces dermatitidis. There was a persistent leukocytosis ranging from 15,000 to 20,000 per cu. mm. accompanied by a 6 to 10 per cent eosinophilia on smear.

Therapy with stilbamidine was instituted June 9, 1952. Two courses, totaling 4.85 gm., with an interval rest period were given. This was accompanied by rapid clearance of the skin lesions and a marked improvement in the patient's general condition. There was no further recurrence of the prostatic abscess. By August 12, 1952, chest roentgenogram had showed considerable clearing of the infiltrative pulmonary lesion. The patient was discharged September 17, 1952.

Three weeks after discharge the patient was readmitted with recurrent skin lesions on the face, a left epididymitis, and a severe right epididymo-orchitis. Again positive cultures were obtained from scrapings of the skin lesions. Spinal fluid and multiple sputum cultures were negative. Under stilbamidine coverage, bilateral epididymo-orchiectomy was performed on October 24, 1952. B. dermatitidis was recovered from the pathologic tissue. A total of 3.15 gm. of stilbamidine was administered on this admission, with clearance of the skin lesions by November 5, 1952, and complete clearance of the residual radiographic pulmonary changes by December 2, 1952.

During the next two and a half years the patient was seen at frequent intervals. Except for complaints of mild generalized weakness and frequent minor infections, he remained well. Voided urine cultures were positive for B. dermatitidis on August 10, 1954, and January 21, 1955. Throughout this period the patient had a persistent eosinophilia of 6 to 9 per cent and the blood pressure ranged from 90/60 to 120/70 mm. Hg. No cutaneous pigmentation was noted.

On June 6, 1955, the patient was readmitted to the hospital with recurrent skin lesions on the cheek which were positive on scraping for B. dermatitidis. The skin test sensitivity was negative and a complement fixation test was positive 1:16 on July 19, 1955. The voided urine was positive and catheterized urine negative for B. dermatitidis. There was no evidence of recurrent pulmonary lesions. A total of 6.45 gm. of 2-hydroxystilbamidine was administered, with clearing of the skin lesions. Cultures of the urine for fungi were negative. During this period of hospitalization, extending to October 13, 1955, the patient noted increasing weakness, mild anorexia and occasional nausea and vomiting. The blood pressure ranged from 80/60 to 92/72 mm. Hg.

During the following year there was no obvious evidence of recurrence of blastomycosis, but the patient complained of increasing anorexia and weakness, with occasional nausea and vomiting. Pigmentation was first noted by the family in the summer of 1956 and was attributed to sun tanning. Dental extractions in October 1956 were followed by a three-day period of severe prostration accompanied by marked anorexia, nausea and vomiting.

On readmission to the hospital on December 6, 1956, the patient had the full-blown picture of Addison's disease with impending crisis. The characteristic pigmentation of Addison's disease was present, and contrasted sharply with the scars of the earlier cutaneous lesions of blastomycosis. This was accompanied by marked weakness, persistent nausea and vomiting and hypotension ranging from 90/70 to 70/50 mm. Hg. The urinalysis was essentially normal, as was a blood count except for an 8 per cent eosinophilia. Serological tests likewise were negative. Sputum, urine and spinal fluid cultures were negative for B. dermatitidis. Blood studies showed a urea nitrogen of 40 mg. per cent, creatinine 3.4 mg. per cent, fasting blood sugar 116 mg. per cent, serum sodium 126 mEq./L., serum potassium 5.4 mEq./L., and serum chlorides 98 mEq./L. A blastomycin skin test was negative. Fasting eosinophil counts on successive days were 1,122 and 866 per cu. mm. Following the intravenous injection of 25 mg. of ACTH over a six-hour period on each day, there was a drop to 1,109 and a rise to 969 per cu. mm., respectively. Collodion agglutination and complement fixation tests were negative for blastomycosis. The twenty-four hour urinary excretion of 17 ketosteroids was 1.8 mg.

Treatment was instituted immediately with the usual forms of therapy, including intravenous hydrocortisone, intramuscular cortisone with supplemental desoxycorticosterone acetate, and intravenous infusions of glucose and saline solutions. With the institution of steroid therapy, a concurrent course of 2-hydroxystilbamidine, totaling 4.5 gm. was given. The response to therapy was striking. It has been possible to maintain this patient on a regimen of 25 to 37½ mg. of cortisone daily supplemented by 3 gm. of sodium chloride. There has been no further evidence of recurrence of active blastomycotic lesions at this writing, twenty-two months after his admission with Addisonian crisis.

COMMENTS

Recent studies have focused attention upon the systemic mycotic infections as etiologic agents

in the production of chronic adrenal cortical insufficiency. Crispell et al. [7] in a recent review found thirty-six cases of adrenal involvement proved by autopsy and fifteen with clinical symptoms suggestive of adrenal insufficiency, but not verified by laboratory tests, among 103 cases of disseminated histoplasmosis. Maloney [8] pointed out that adrenal involvement occurred in sixteen of fifty cases of disseminated coccidioidomycosis, although clinical Addison's disease was rarely described. We believe that the incidence of adrenal involvement in blastomycosis may be higher than that found thus far in the literature.

Maloney postulates that the paucity of clinical cases of Addison's disease in systemic mycotic infections, which apparently rather commonly affect the adrenal glands, is explainable in one of two ways: (1) Patients with these diseases may succumb from dissemination of the disease to other vital parts before the adrenals are completely destroyed. (2) It is estimated that over 95 per cent of the total adrenal cortical tissue must be destroyed before the typical symptom complex characterizing Addison's disease appears. Complete destruction of both glands by the deep mycoses has been reported rarely.

To these reasons we would add a third: Symptoms of adrenal insufficiency may be submerged in the total clinical picture of the systemic mycotic infection, or erroneously attributed to the fungus infection itself. In the presence of diseases which until recently were considered to be fatal in a high proportion of cases, it would be easy to ascribe non-specific gastrointestinal complaints, asthenia and hypotension, particularly in the absence of pigmentation, to the primary disorder. Establishing the diagnosis of Addison's disease ordinarily is simple. Occasionally, however, it is possible to overlook even the obvious in the absence of a reasonable degree of suspicion. This played a part in delaying diagnosis and in postponing treatment in our patient.

Spontaneous healing or regression of blastomycotic lesions may occur at varying rates according to site of involvement, and persistence of active lesions at some sites after regression elsewhere under the influence of chemotherapy (aromatic diamidines) has been observed. The lesions responding most rapidly to chemotherapy (and which occasionally regress spontaneously) are the non-cavitary pneumonic pulmonary lesions. Not uncommonly, genitourinary, cutaneous or cavitary pulmonary lesions may remain persistently active despite chemotherapy. Lesions may recur after apparently successful therapy with either stilbamidine or 2-hydroxystilbamidine. In a recent review of 113 patients with blastomycosis treated with the aromatic diamidines [9], a recurrence rate of 33 per cent was noted among those patients who had been followed up one year or more after treatment. It is important to note that constitutional symptoms are not a necessary accompaniment of an active but localized lesion of blastomycosis.

The reported experience with amphotericin-B, although promising, is too sparse to draw final conclusions as yet regarding the efficacy of this drug in the treatment of blastomycosis.

Since adrenal destruction due to blastomycosis has been demonstrated in an appreciable percentage of autopsy cases, it is reasonable to postulate that in disseminated blastomycosis, adrenal involvement may occur in the form of an active localized lesion, without systemic symptoms, even after regression of the lesions elsewhere. Depending upon the degree of cortical destruction, latent insufficiency may occasionally occur and more rarely chronic adrenal cortical insufficiency (Addison's disease) may result. It is possible in the rapidly progressive and fatal form of North American blastomycosis that the manifestations of acute adrenal cortical insufficiency may be obscured or overlooked. In the presence of unexplained deterioration, therefore, in either the acute or chronic recurring form of North American blastomycosis, appropriate adrenal cortical function studies should be carried out. Since various stress reactions may precipitate acute episodes of adrenal cortical insufficiency, it is also important, in the asymptomatic patient, to be aware of the existence of latent degrees of cortical insufficiency. In view of the relative simplicity and ready availability of laboratory technics designed to detect varying degrees of adrenal cortical insufficiency, no case should remain undiscovered if its existence is suspected. With adequate replacement therapy, treatment may be life-saving.

SUMMARY

The clinical course of a patient with proved systemic blastomycosis, in whom Addison's disease developed, is reported. Since the inci-

dence of involvement at autopsy of the adrenals with blastomycosis is appreciable (between 5 and 10 per cent) this possibility should be considered in patients with systemic blastomycosis whether they are symptomatic or not, and appropriate studies undertaken to evaluate the adequacy of adrenal cortical function.

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Addison's Disease Secondary to Adrenocortical Destruction by Metastatic Carcinoma of the Breast*

JOHN A. GALLOWAY, A.B., M.D. *and* WILLIAM H. PERLOFF, M.D.
Philadelphia, Pennsylvania

A FORTY-SIX year old white woman (M. R.) was admitted to the hospital in August 1956 because of a lump in the breast. A radical mastectomy was performed and followed by local roentgen rays, radon seed and radiocobalt radiation therapy. The pathologist reported, "Carcinoma, inflammatory type." The patient's blood pressure before discharge was 142 mm. Hg systolic, 86 mm. Hg diastolic. Her weight was 154 pounds. When seen again in January 1958 the blood pressure was 108 systolic over 64 diastolic and her weight was 148 pounds. Her skin showed areas of grey-brown pigmentation, particularly in the creases of the hands and knuckles. Her complaints were chronic unremitting fatigue, pain in the lower part of her back and right hip, and persistent cough. Roentgenographic examination revealed a "cannon-ball" mass in the right side of the mid-thorax and a destructive lesion in the right ileum. One week later bilateral adrenalectomy was performed. The glands were approximately two times normal size; the left gland weighed 19.7 gm. and the right gland weighed 14.6 gm. Approximately 95 per cent of the glands were replaced by opaque, pinkish grey tumor tissue. The intact cortex was bright yellow. The patient was treated with cortisone and her condition temporarily improved. The blood pressure remained at levels of 118 to 130 mm. Hg systolic, 78 to 82 diastolic. The downhill course was relentless, however, and she died on April 28, 1958. A postmortem examination was not made. Despite the absence of laboratory evidence, the clinical findings strongly suggested the presence of Addison's disease, secondary to adrenocortical replacement by neoplastic tissue prior to surgery.

In the light of this case, a literature review was undertaken of reports and statistics on the frequency of metastasis of epithelial tumors to the adrenal glands. The incidence of adrenal insufficiency from metastatic destruction of the cortex was also studied.

Metastasis of carcinomas to the adrenal glands is a common finding at autopsy. Glomset [*1*] in 1938 found adrenal metastases in 13 per cent of 821 patients with malignant tumors. Burke [*2*] in 1934 reported that adrenal metastases were present in 49 (13 per cent) of 371 patients with tumors. He found metastases from primary tumors of the esophagus, stomach, testicle, penis, prostate, uterus, thyroid, tongue, bladder and pancreas in either one or both adrenals. In 1948 [*3*] a patient with adrenal metastasis from carcinoma of the gallbladder was described.

Metastasis of carcinoma of the breast to the adrenals occurs with a frequency that is equaled or exceeded only by bronchogenic carcinoma. Saphir and Parker [*4*] reviewed the literature in 1941, including a series compiled in 1880. (Table I.) In their own study of forty-three instances of carcinoma of the breast they found adrenal involvement in nineteen cases, in thirteen of which the tumor was recognized on gross examination. In seven instances both adrenals were involved. They concluded that the adrenal gland was the third most common metastatic site for carcinoma of the breast, following the lung (twenty-eight cases) and the liver (twenty-four patients). Burke [*2*] reported nine cases of adrenal involvement in thirty-five women with carcinoma of the breast and Willis [*5*] in 1941 described forty-five women with carcinoma of the breast, 9 of whom showed adrenal metastases. Clark and Rowntree [*6*] stated in

* From the Departments of Medicine and Endocrinology, Temple University School of Medicine and Medical Center, Philadelphia, Pennsylvania.

TABLE I

CHRONOLOGICAL SUMMARY OF REPORTED INCIDENCE OF METASTASES FROM CARCINOMA OF THE BREAST TO THE ADRENAL GLAND OR GLANDS, MODIFIED FROM SAPHIR AND PARKER [4] 1941

Series from	Year	Total Cases	Adrenal Metastases	Per cent
von Torok and Wittelshofer	1880	336	6	1.8
Gross	1888	114	1	0.9
Paget	1889	735	30	3.8
Williams	1894	44	2	4.5
Campiche and Lazarus-Barlow	1904	470	35	9.7
Warren and Whitham	1933	160	50	31.2
Glomset	1938	43	25	58.2
Saphir and Parker	1941	43	19	44.2

1934 that cancer of the breast produced adrenal metastases more frequently than any other type of tumor.

More recent statistical surveys of adrenal tumor metastases compare the incidence of carcinoma of the lung and breast. (Table II.) In 1950 Abrams, Spiro and Goldstein [7] found the incidence to be 35.6 per cent for cancer of the lung and 53.9 per cent for cancer of the breast, Bullock and Hirst [8] reported 28.7 per cent for lung and 12.8 per cent for breast and Sahagian-Edwards and Holland [9], reporting in 1954, found 42 per cent for lung and 34 per cent for breast.

Except for one case, admittedly questionable, which was reported by Thomas Addison [10] in 1849, we have found no reported instance of adrenal insufficiency from carcinoma of the breast. In 1952 Butterly et al. [11] reported three and possibly four cases of Addison's disease resulting from destruction of the adrenal glands secondary to bronchogenic carcinoma. In a review of the literature they could find only seven cases reported in fifty years; four from bronchogenic carcinoma, one from gastric carcinoma, and two cases in which the type of tumor was not mentioned. In 1952 Wallach and Scharfman [12] reported an additional case and the most recent reports of Sahagian-Edwards and Holland [9] cited four more cases in 1954.

It is not quite clear why adrenocortical insufficiency does not develop more frequently in such patients. A possible explanation is that the course of cancer of the breast is terminated

TABLE II

A COMPARISON OF THE FREQUENCY OF METASTASES TO THE ADRENAL GLANDS OF CARCINOMAS FROM BRONCHUS AND BREAST, MODIFIED FROM BULLOCK AND HIRST [8]

Series from	Bronchus			Breast		
	No. Cases	Adrenals	Per cent	No. Cases	Adrenals	Per cent
Abrams, Spiro and Goldstein	160	57	35.6	167	90	53.9
Bullock and Hirst	397	114	28.7	186	24	12.8
Sahagian-Edwards and Holland	283	119	42	178	61	34

before sufficient adrenal cortex is compromised. Wells [13] stated in 1930 that 90 per cent of patients with Addison's disease show complete destruction of the adrenal gland. Guttman [14] in the same year reported that bilateral metastatic tumors seldom give rise to Addison's disease. He noted that although little adrenal tissue is recognized on gross examination, "one finds abundant nests of surviving parenchyma microscopically." He concluded that "the incomplete destruction of the suprarenal glands may account for the absence of symptoms of Addison's disease." Whatever the mechanism, it would appear that the rapid death of some patients with cancer of the breast may be hastened by occult Addison's disease.

SUMMARY

A case of carcinoma of the breast with metastatic destruction of the adrenal glands, producing clinical evidence of Addison's disease, is presented. An analysis of the literature indicates a high incidence of metastasis of cancer of the breast to the adrenals, of the same order of frequency as bronchogenic carcinoma, but the incidence of Addison's disease is low.

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Isolated Congenital Pulmonic Valvular Regurgitation*

Diagnosis by Cardiac Catheterization and Angiocardiography

N. Perryman Collins, M.D., Eugene Braunwald, M.D. *and* Andrew G. Morrow, M.D.

Bethesda, Maryland

Acquired organic pulmonic valvular regurgitation is not an uncommon lesion. It is seen following bacterial endocarditis, rheumatic fever and syphilis. Functionally it is frequently observed in patients with pulmonary hypertension and presumably results from dilatation of the pulmonary artery. Isolated congenital pulmonic regurgitation, however, is extremely rare, and results either from congenital malformation or absence of the valve cusps or from idiopathic dilatation of the pulmonary artery.

In the 1,000 cases of congenital heart disease studied by Abbott [*1*] there were only eight cases of primary pulmonary insufficiency. Six of these cases were associated with idiopathic dilatation of the pulmonary artery; whereas only two were secondary to anomalies of the valve cusps. Pulmonary insufficiency occurs only in the minority of patients with idiopathic dilatation of the pulmonary artery [*2*] and, apparently, is even less common in patients with malformation of the valve cusps. Kissin [*3*] reviewed the records of 151 patients in whom the heart had four-cusped pulmonic valves; there were only three who appeared to have had pulmonic insufficiency. Ford et al. [*4*] found sixteen cases of isolated bicuspid pulmonic valves described in the literature, in four of these there was evidence of pulmonic regurgitation.

Most descriptions of isolated pulmonary regurgitation have been based on postmortem studies, in some of which a retrospective review of the clinical data suggested the diagnosis. In the past several years, however, there have been isolated reports in which this anomaly was suspected during life [*2,4–7*]. It is the purpose of this paper to present a patient in whom the diagnosis was made unequivocally at the time of right heart catheterization and confirmed by angiocardiography.

CASE REPORT

J. H. (Clinical Center 02-14-53), a thirty-six year old housewife, had been known to have a heart murmur since early childhood. She had been entirely asymptomatic and had undergone three pregnancies without difficulty. Eleven months prior to admission she began to experience mild exertional dyspnea and easy fatiguability. There was no history suggestive of rheumatic fever or bacterial endocarditis. She was admitted to a university medical center and underwent two right heart catheterizations and two transbronchial left heart catheterizations the results of which were reported to be normal. In spite of these studies it was thought that a small left-to-right shunt was present and she was referred to the National Heart Institute for further diagnostic study.

On physical examination she was found to be well developed and did not appear to be ill. The pertinent physical findings were limited to the heart. The point of maximal impulse was in the fifth left intercostal space in the left midclavicular line; there was no enlargement to percussion, although there was a slight right ventricular lift. A diastolic thrill was felt in the third and fourth left intercostal spaces at the left sternal border. Normal sinus rhythm was present and the heart sounds were of good quality. The second pulmonic sound exhibited normal splitting during the respiratory cycle. At the left sternal border there was a short, grade 1 (grade 6 scale) systolic murmur and a louder (grade 3 (grade 6 scale)), low-pitched murmur most prominent in mid-diastole. (Fig. 1.) This diastolic murmur was transmitted over the entire precordium, but was loudest in the third and fourth left intercostal spaces. The lungs were clear, there was no evidence of heart failure, and the systemic blood pressure was normal.

Radiographic examination revealed the heart size to be normal. There was slight enlargement of the

* From the Clinic of Surgery, National Heart Institute, Bethesda, Maryland.

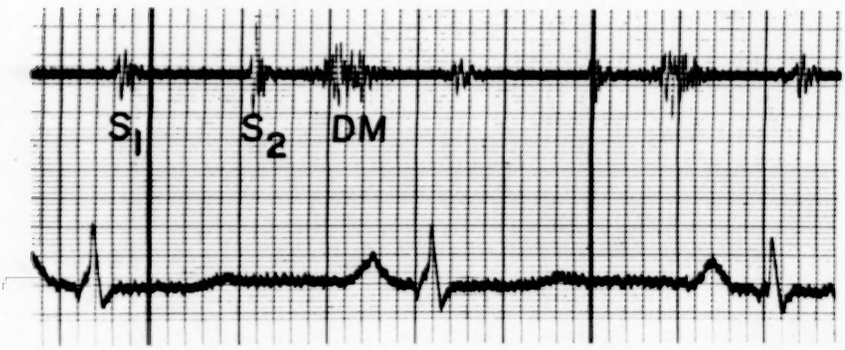


FIG. 1. Patient J. H. Phonocardiogram taken at third intercostal space at left sternal edge. S_1 and S_2 represent the two heart sounds. DM represents the mid-diastolic murmur.

pulmonary artery and its major branches. (Fig. 2.) At fluoroscopic examination the pulmonary artery pulsations were quite prominent. The electrocardiogram demonstrated a normal sinus rhythm, vertical position with rightward direction of the terminal forces. (Fig. 3.) On the basis of these clinical findings the presence of isolated pulmonary regurgitation was considered likely.

At right heart catheterization a double lumen catheter was passed into the heart with the distal lumen lying in the main pulmonary artery and the proximal lumen in the right ventricle. Simultaneous pressures from these two areas were recorded by means of two equisensitive Statham pressure transducers adjusted to identical baselines. Except for identical systolic and diastolic pressures in the right ventricle and pulmonary artery (28/7 mm. Hg) (Fig. 4), the catheterization findings were normal. (Table I.) The nitrous oxide test [*8*] in the pulmonary artery was 2 per cent, indicating the absence of any left-to-right shunt.

A selective angiocardiogram was performed with the injection of 47 cc. of 70 per cent Urokon® through a No. 8 Lehman catheter into the main pulmonary artery by means of a Giedlund power syringe. Simultaneous anteroposterior and lateral films were exposed at a rate of six per second with a Schonander angiocardiographic apparatus. Marked regurgitation of dye from the pulmonary artery into a dilated right ventricle was noted. (Fig. 5.) The regurgitant jet appeared to be localized to the anterior portion of the valve and no valve leaflet could be identified in this area. The diagnosis of pulmonary regurgitation can be established by this technic since right ventricular filling has not been noted following injections distal to presumably normal and competent valves.

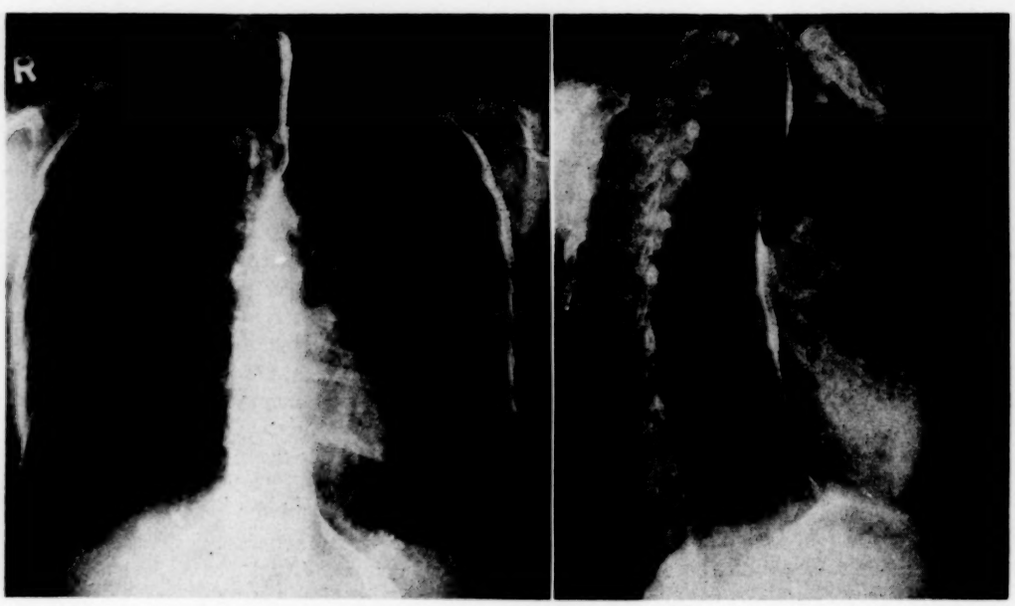


FIG. 2. Posteroanterior and lateral roentgenograms of patient J. H.

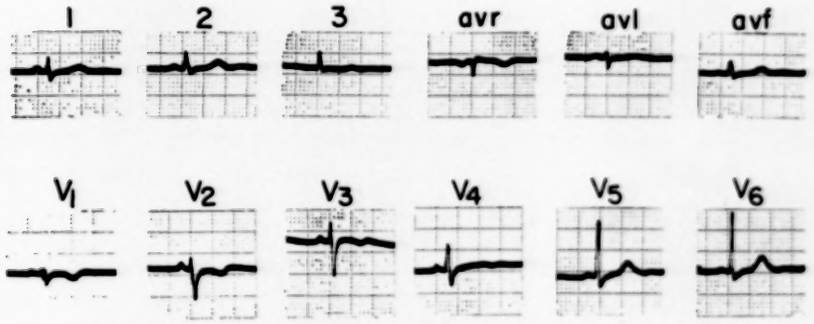


FIG. 3. Electrocardiogram of patient J. H.

TABLE 1
SUMMARY OF DATA OBTAINED AT RIGHT HEART CATHETERIZATION (PRESSURES IN MM. HG)

Site	Systolic/Diastolic	Mean
Pulmonary "capillary"	15/9	11
Pulmonary artery	28/7	13
Right ventricle	28/7	..
Right atrium	....	2

Oxygen consumption	
Rest*	140 cc./min./M.^{2}
Exercise	274 cc./min./M.^{2}
Cardiac output	
Rest	2.55 L./min./M.^{2}
Exercise	3.87 L./min./M.^{2}
Pulmonary vascular resistance	
Rest	44 dynes sec. cm.$^{-5}$
Exercise	128 dynes sec. cm.$^{-5}$
Arterial oxygen saturation	95.0%

* Average of two values.

COMMENTS

There have been three other instances reported in which the diagnosis of isolated congenital pulmonic regurgitation was established antemortem when similar pressure pulses in the right ventricle and pulmonary artery were noted [*4,6,7*]. In the patient described in this report the following clinical features suggested the diagnosis: (1) the history of a murmur discovered in childhood without a history of rheumatic fever; (2) the absence of significant symptoms; (3) evidence of increased right ventricular activity on palpation of the chest; (4) prominence of the pulmonary artery on radiologic examination; and (5) a low-pitched mid-diastolic murmur and thrill along the left sternal border unaccompanied by a widened systemic arterial pulse pressure, by a prominent systolic murmur, or an accentuated pulmonary second sound. It is of interest that there is frequently a short gap between the second heart sound and

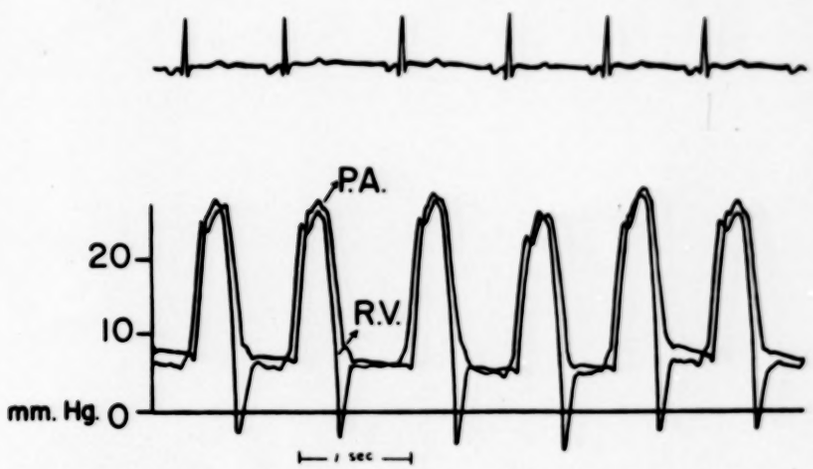


FIG. 4. Simultaneous pulmonary artery (PA) and right ventricular (RV) pressures obtained at right heart catheterization.

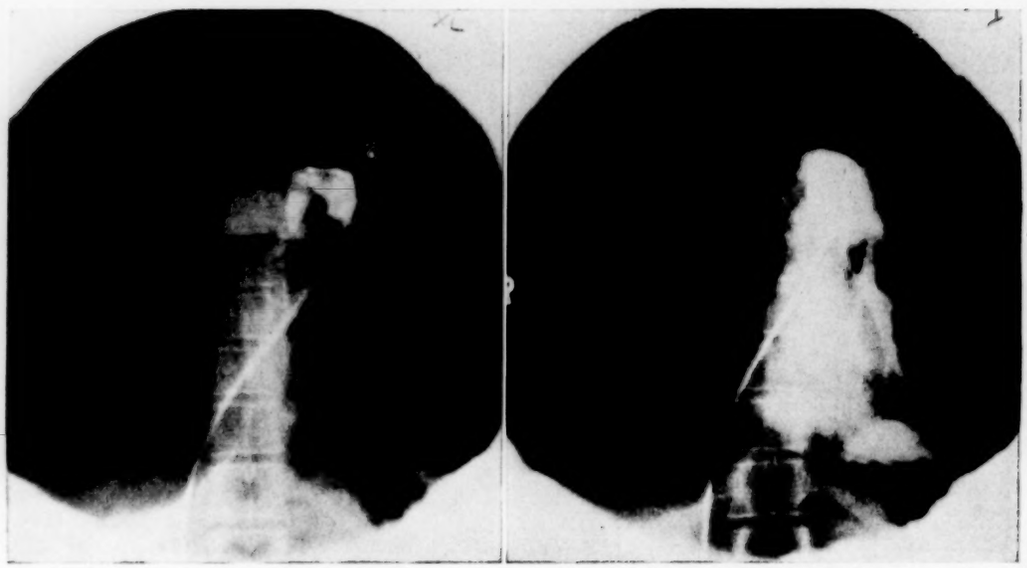


FIG. 5A. Anteroposterior angiocardiogram at one-half (left) and two (right) seconds following injection into the pulmonary artery.

the onset of the diastolic murmur in pulmonary regurgitation [*2,4,9*]. This murmur may be of the crescendo-decrescendo type [*10,11*] (Fig. 1) and in the absence of pulmonary hypertension is usually low-pitched [*11*].

The definitive diagnosis, however, was made by cardiac catheterization and facilitated by the simultaneous recording of pulmonary artery and right ventricular pressures. In addition, the diagnosis was confirmed by selective angiocardiography, which clearly demonstrated reflux of dye from the pulmonary artery to the right ventricle and demonstrated only moderate dilatation of the pulmonary artery. This latter finding, together with the apparent deficiency of valve leaflet anteriorly, suggests that the pulmonary regurgitation in this patient is secondary to a primary valvular anomaly.

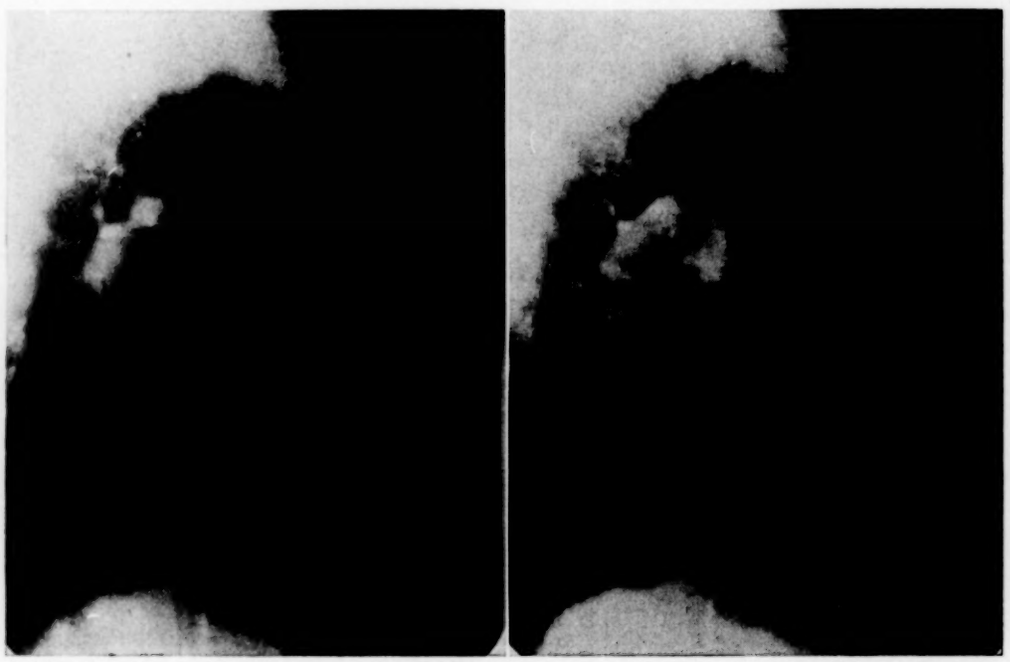


FIG. 5B. Lateral angiocardiogram at one-half (left) and two (right) seconds following injection into the pulmonary artery. Reflux of dye into the right ventricle is seen on the two-second film.

The physiologic consequences of pulmonary valvular regurgitation have not been completely clarified. It is clear that extensive experimentally produced pulmonary valvular damage in the dog is usually tolerated well [*12,13*] and certainly better than similar degrees of aortic valve damage [*14*]. Fowler and Duchesne, however, have recently demonstrated that this lesion is not entirely innocuous [*15*]. In dogs which were studied twelve to eighteen months after the lesion was induced there was no evidence of right-sided heart failure nor limitation of activity. However, right ventricular dilatation occurred. The cardiac output, which was abnormally low at rest could be increased by electrical stimulation of the extremities. Kay and Thomas also observed right ventricular dilatation in dogs sacrificed nineteen to thirty-one months after complete excision of the pulmonary valve cusps [*16*].

The clinical consequences of pulmonary regurgitation are not usually serious. Two patients, aged seven years, with isolated pulmonary regurgitation were entirely asymptomatic [*2,7*]. Another patient, twenty years of age, had mild exertional dyspnea [*6*]. In the patient described in this report it was not clear whether the mild symptoms were related to the presence of the lesion. The reflux of blood from pulmonary artery to right ventricle evidently resulted in the elevation of the right ventricular end-diastolic pressure to the upper limits of normal. However, the resulting cardiac output was within normal limits, and could be elevated normally during exercise. The production of pulmonary regurgitation in the course of pulmonary valvulotomy is not generally considered to be a serious complication [*17*]. It should, however, be noted that, of the four patients previously described, one patient with isolated congenital pulmonary regurgitation died suddenly at the age of forty-four years after progression of the severity of congestive heart failure [*4*].

Hemodynamically, the effects of isolated pulmonary valvular regurgitation on the heart itself are quite analogous to those of atrial septal defect, since both lesions are associated with an increase in right ventricular output. It is of interest that patients generally tolerate atrial septal defects well until pulmonary vascular changes, presumably related to increased pulmonary blood flow, result in pulmonary hypertension. Only when this additional burden is imposed upon the right ventricle does failure ensue.

SUMMARY

A patient with congenital isolated pulmonic valvular regurgitation is described. The diagnosis was established when identical right ventricular and pulmonary artery pressures were noted during the course of cardiac catheterization. A selective angiocardiogram with pulmonary artery injection revealed reflux of dye from the pulmonary artery into the right ventricle, confirming the diagnosis. The lesion was not associated with any significant symptoms.

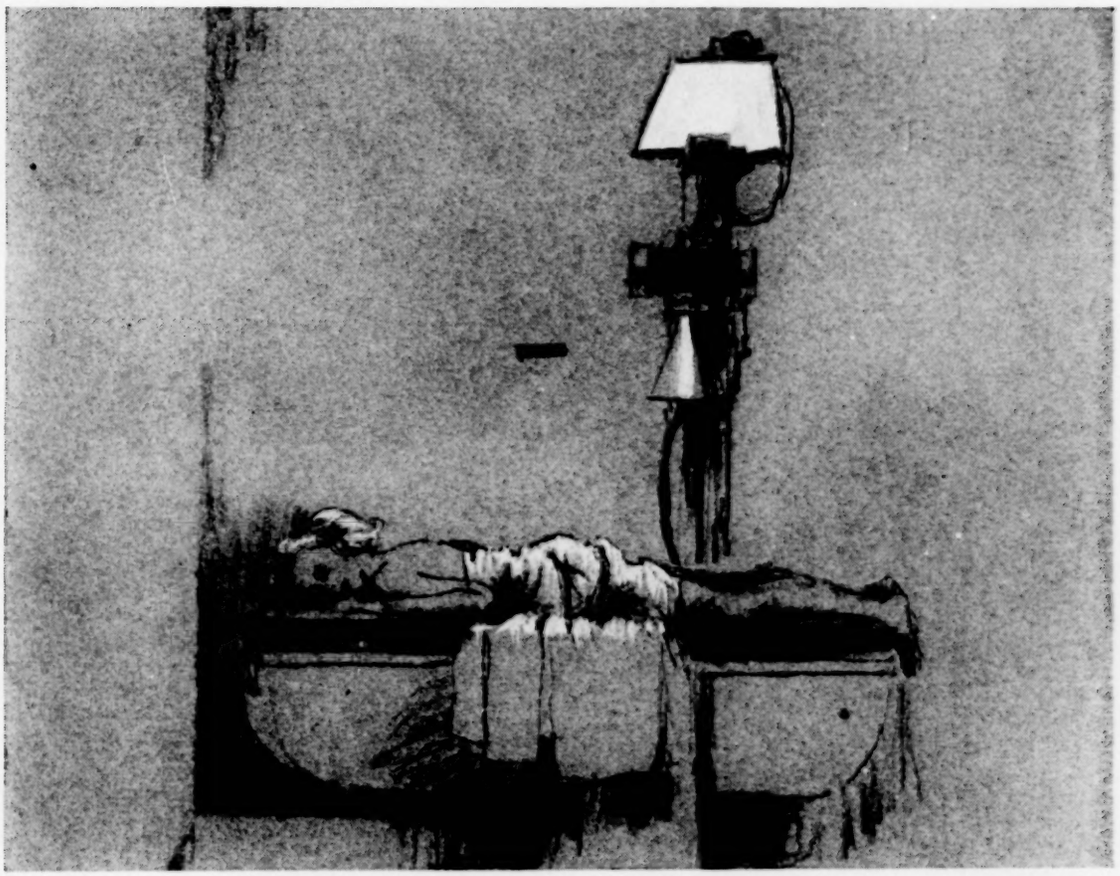
ADDENDUM

Since this paper was submitted, another patient with isolated congenital pulmonic valve disease has been studied. This patient was an asymptomatic sixteen year old boy with a systolic and diastolic murmur in the pulmonic area, who had right ventricular hypertrophy and prominence of the pulmonary outflow tract on x-ray examination. No cardiac shunts were present. The pressure in the pulmonary artery was 22/8 mm. Hg and 48/8 mm. Hg in the right ventricle. Severe pulmonic regurgitation was present. This was demonstrated by the prompt appearance in the right ventricle of cardio-green dye and radioactive krypton (Kr^{85}) following the injection of these indicators into the pulmonary artery [*18*].

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The chemical cha ristocetins are not c though they are kn teric substances con phenolic groups a ristocetin A and ris molecules with m the vicinity of 4000 have good stability pH range of bloo SPONTIN is a ly tion, derived fr material, represe ristocetins A an

Antimicrobial tion against gra ganisms, SPON effective than able antibiotics

Against pne cocci (except s cocci) the anti tericidal at th concentration hibits the gro also kills the

This obse for the majo lococci. Ho staphylococ have been t centration s minimum i produce a this reaso SPONTIN i for the trea and enterococcal infections.

Cultures of staphylococcus aureus, which are resistant to other antibiotics have been shown to be sensitive to SPONTIN. There has been no case reported in which a staphylococcal or enterococcal strain has exhibited a SPONTIN

pH range of blood and SPONTIN is a lyophilized preparation, derived from pure crystalline material, representing a mixture of ristocetins A and B.

Antimicrobial Properties. In its action against gram-positive coccal or- SPONTIN is notably more tly avail-

d strepto- of entero- riably bac- osage. The which in- organisms

holds true s of staphy- e strains of ococci which quired a con- gher than the centration to effect. It is for her dosage of recommended staphylococcal tions.

coccus aureus, other antibi- to be sensitive s been no case taphylococcal or has exhibited a SPONTIN.

that the antibi- NTIN is enhanced gamma globulin. supported by the *vivo* activity of imes greater than from the *in vitro*

estigators* have re- cal response follow- ration of SPONTIN dies have shown a vity on the part of ganism. Satisfactory may be expected sm requires up to 25 ONTIN for inhibition llowing table shows nsitivities of different he major pathogenic groups.

Summary and Conclusions

Major use has been treating staphylococcic infections. Of the total 333 cases, approximately one-third was treated for pneumonia; of these over 80% were either cured or improved. About 70% of these pneumonias were caused by staphylococci.

The next largest group included 46 patients with subacute bacterial endocarditis. About 50% of these infections were identified as staphylococcic and a further 15% as enterococcic. Other infections included 38 cases of septicemia, 32 abscesses and 24 patients with osteomyelitis.

The administration of SPONTIN brought about a cure in 60% of all the cases reviewed and improvement in a further 17%.

Side-effects were seldom troublesome when a daily dose of 2 Gm. was not exceeded. The incidence rose as the dosage was increased. The most disturbing side-effect after administration of SPONTIN has been neutropenia. However, in all instances this has responded to either discontinuance of medication or reduction in dose.

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ready for immediate use to soothe, protect, stimulate healing in—

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(decubitus, diabetic, varicose)
lacerated, denuded, raw surface tissues



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Therapeutic vitamins in the "therapeutic" jar

Any severe disease process undermines the nutritional integrity of tissue.[1] To counteract physiologic stress depletion of B and C vitamins, prescribe high potency STRESSCAPS . . . in burns . . . fractures . . . severe infection . . . surgery . . . and in chronic disorders such as arthritis, alcoholism or colitis.

The attractive STRESSCAPS jar also plays an important therapeutic role . . . reminding the patient of his daily dosage . . . assuring adequate intake for full metabolic support.

Each capsule contains:

Thiamine Mononitrate (B_1)	10 mg.
Riboflavin (B_2)	10 mg.
Niacinamide	100 mg.
Ascorbic Acid (C)	300 mg.
Pyridoxine HCl (B_6)	2 mg.
Vitamin B_{12}	4 mcgm.
Folic Acid	1.5 mg.
Calcium Pantothenate	20 mg.
Vitamin K (Menadione)	2 mg.

Average dose 1-2 capsules daily.

STRESSCAPS®

Stress Formula Vitamins Lederle



1. Spies, T. D.: J. A. M. A. 167:675 (June 7) 1958.

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Each Calurin tablet is equivalent to 300 mg. (5 gr.) of acetylsalicylic acid.

(CALCIUM ACETYLSALICYLATE CARBAMIDE)

References: 1. Muir, A.: Aspirin and Gastric Damage, Scientific Exhibit, A.M.A. Convention, Atlantic City, N. J., June 8-12, 1959. 2. Waterson, A. P.: Brit. M.J. 2:1531, 1955. 3. Editorial Comments: The effect of acetylsalicylic acid on the gastric mucosa, Canad. M.A.J. 80:47, 1959. 4. Muir, A., and Cossar, I. A.: Brit. M.J. 2:7, 1955. 5. Muir, A., and Cossar, I. A.: Lancet 1:539, 1959. 6. Schneider, E. M.: Gastroenterology 33:616, 1957. 7. Bayles, T. B., and Tenckhoff, H.: Salicylate Therapy in Rheumatic Diseases, Scientific Exhibit, Ann. Mtg. A.M.A., San Francisco, Calif., June, 1958. 8. Douthwaite, A. H., and Lintott, G. A. M.: Lancet 2:1222, 1938. 9 Batterman, R. C.: New Eng. J.M. 258:213, 1958. 10. Cronk, G. A.: New Eng. J.M. 258:219, 1958. 11. Editorial: Aspirin plain and buffered, Brit. M.J. 1:349, 1959. 12. Smith, P. K.: Plasma concentration of salicylate after the administration of acetylsalicylic acid or calcium acetylsalicylate to human subjects, Report submitted to Smith-Dorsey from the Dept. of Pharmacology, Geo. Washington Univ. School of Medicine, Washington, D. C., Sept. 5, 1958.

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Hycodan®		
Dihydrocodeinone Bitartrate (Warning: May be habit-forming)	5 mg.	6.5 mg.
Homatropine Methylbromide	1.5 mg.	
Pyrilamine Maleate		12.5 mg.
Phenylephrine Hydrochloride		10 mg.
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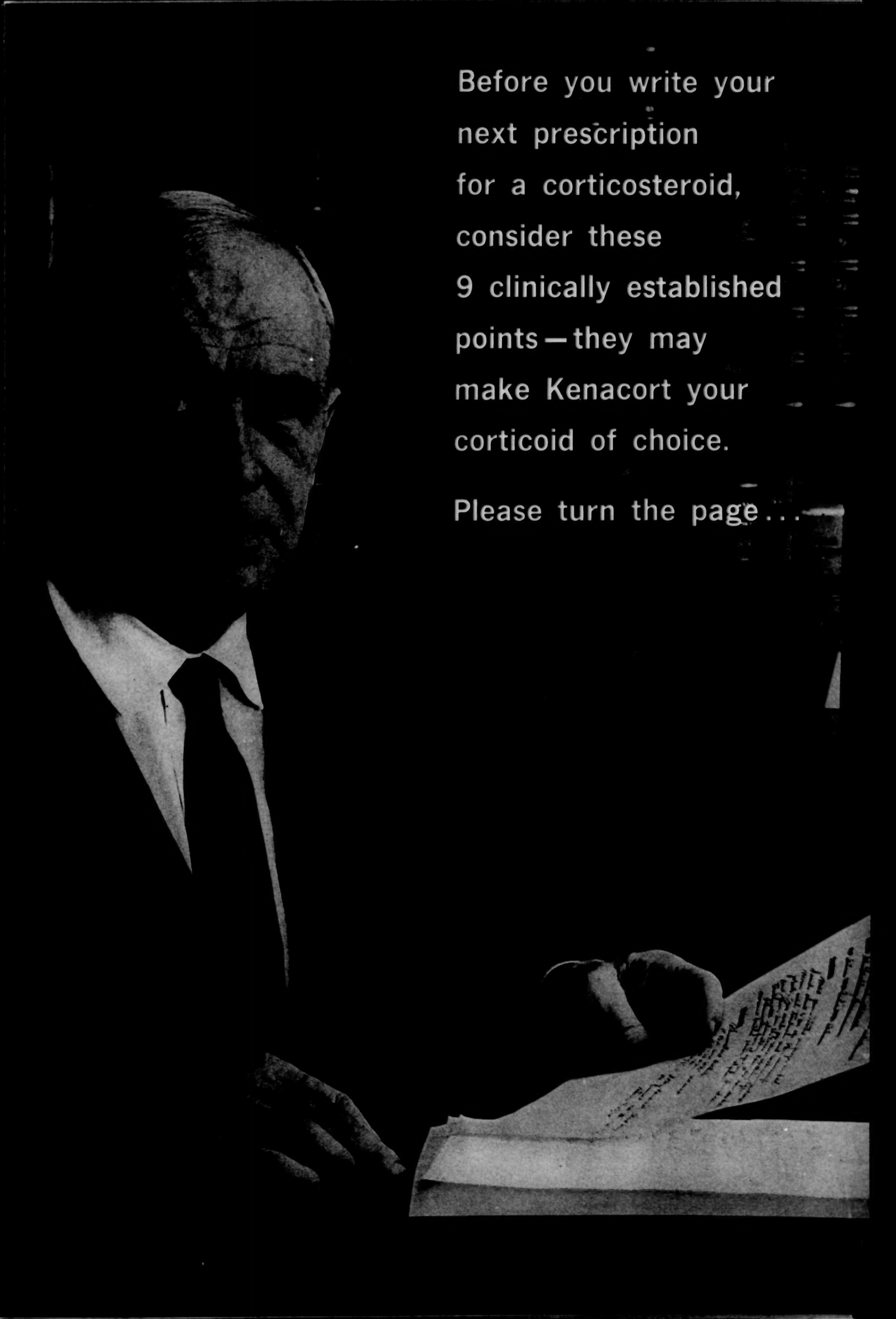
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Allison, J. R., Sr., and Allison, J. R., Jr.:
Monographs on Therapy 3:99 (Oct.) 1958.

pre-prescription point number **2**

continuing therapy—maintenance doses are low

Feinberg, S. M.; Feinberg, A. R., and Fisherman, E. W.:
J. A. M. A. 167:58 (May 3) 1958.

pre-prescription point number **3**

no sodium or water retention—low salt diet not necessary

Hartung, E. F.:
J. A. M. A. 167:973 (June 21) 1958.

pre-prescription point number **4**

absence of edema

Council on Drugs:
J. A. M. A. 169:257 (Jan. 17) 1959.

pre-prescription point number **5**

less likely to create electrolyte disturbance

Bongiovanni, A. M.; Mellman, W. J., and Eberlein, W. R.:
J. Pediat. 53:3 (July) 1958.

pre-prescription point number **6**

no secondary hypertension—no significant change in pulse, respiration, or blood pressure

Shelley, W. B.; Harun, J. S., and Pillsbury, D. M.:
J. A. M. A. 167:959 (June 21) 1958.
Bernsten, C. A., Jr., and others:
New York Rheumatism Association, Annual Meeting, New York, April 9, 1959.

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Available in 1 mg., 2 mg. and 4 mg. scored tablets.

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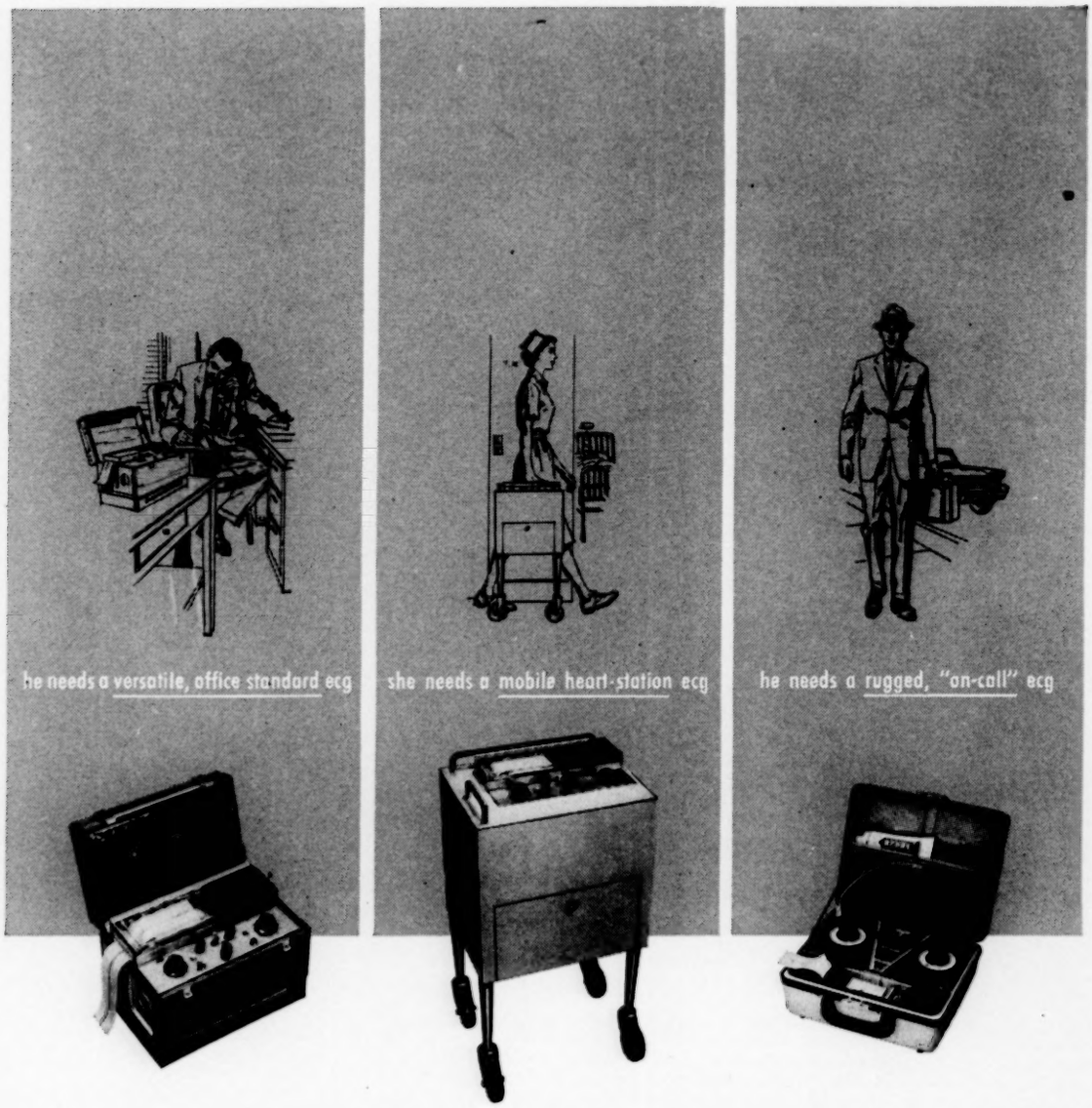
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Shelley, W. B.; Harun, J. S., and Pillsbury, D. M.:
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Council on Drugs:
J. A. M. A. 169:257 (Jan. 17) 1959.

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gastrointestinal complaints infrequent

Hartung, E. F.:
J. A. M. A. 167:973 (June 21) 1958.



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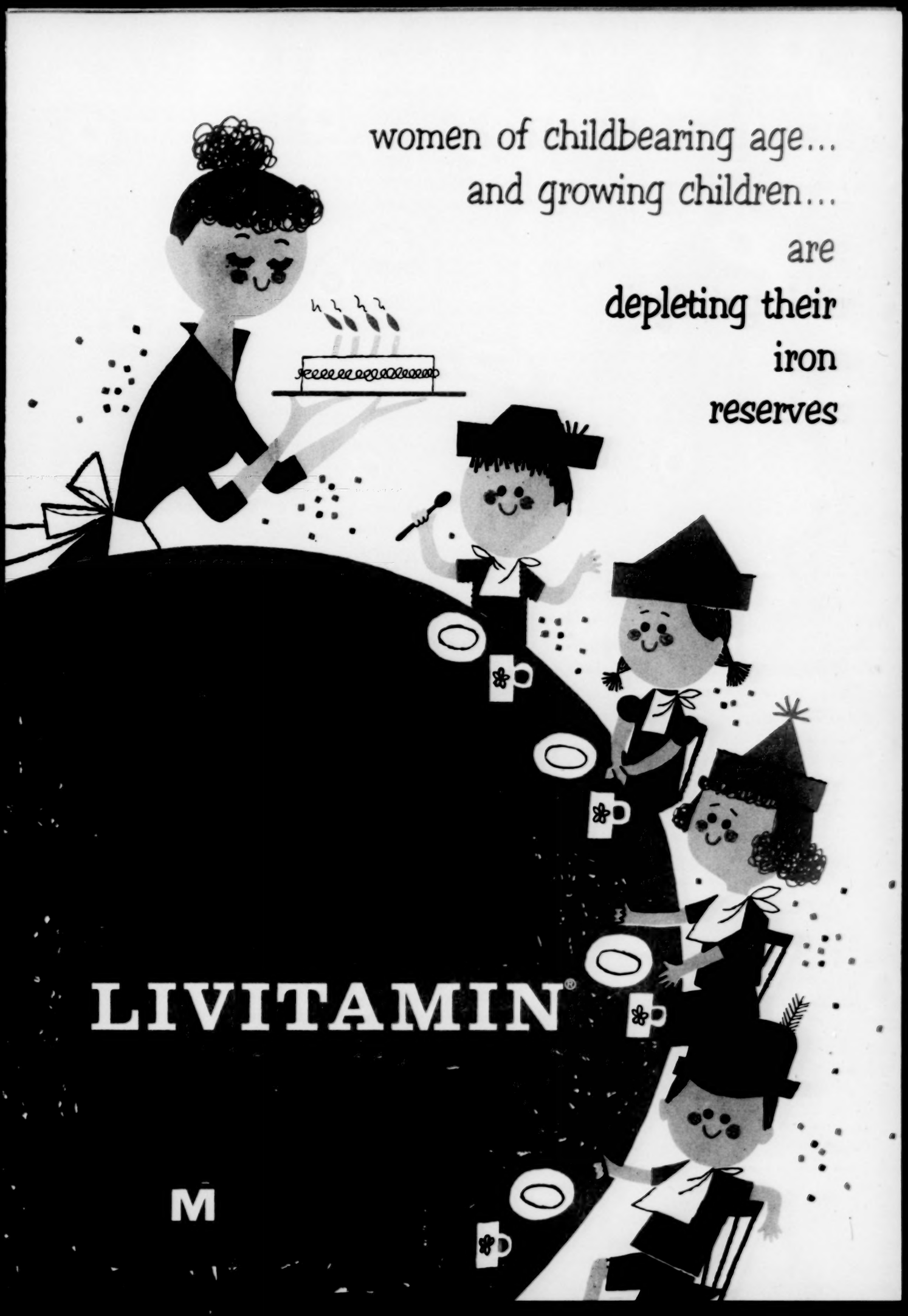
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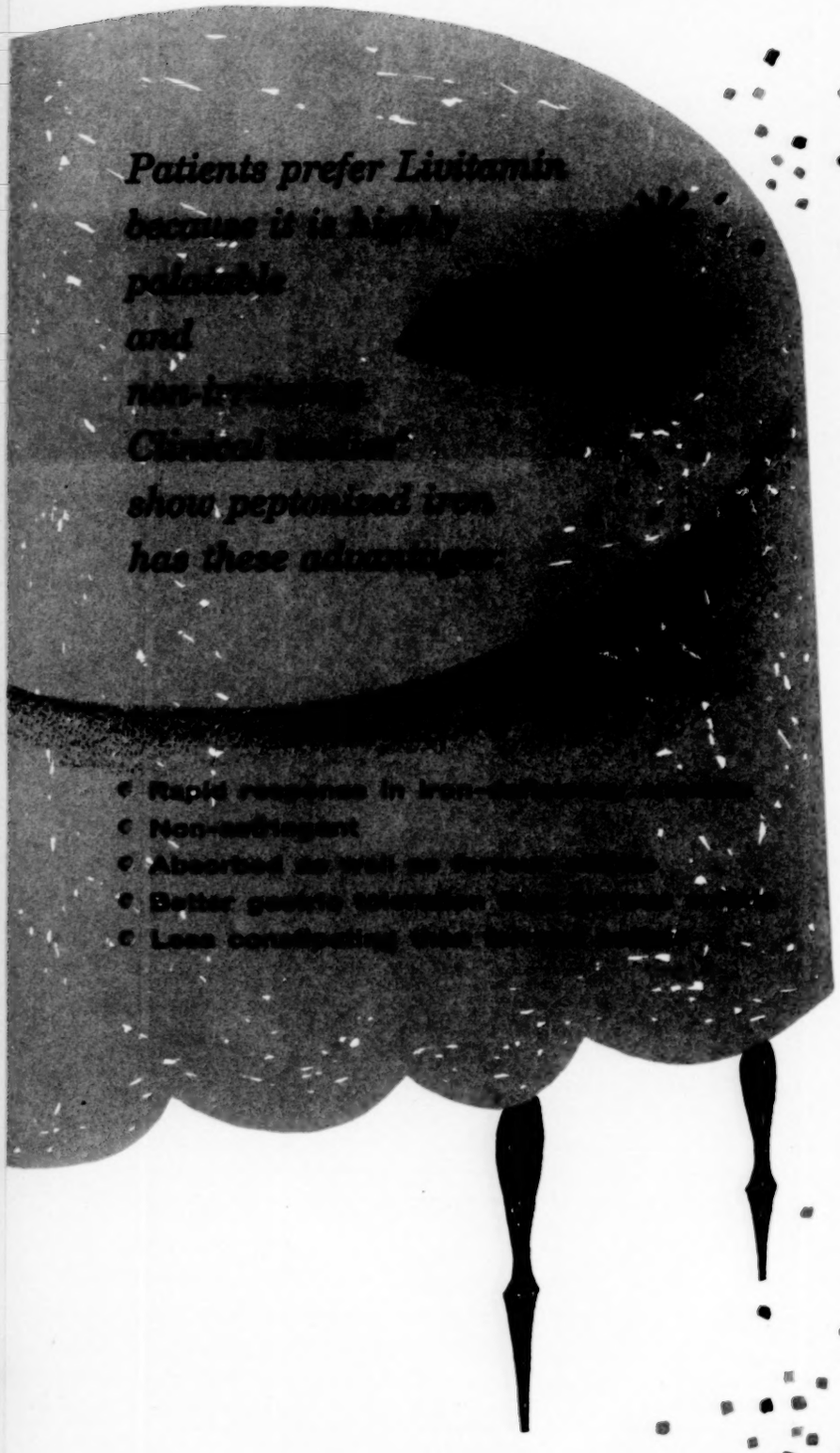
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*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Am. J. Clin. Nutrition 1:35 (Jan.-Feb., 1957).

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Cremomycin® provides rapid relief of virtually all diarrheas

NEOMYCIN—rapidly bactericidal against most intestinal pathogens, but relatively ineffective against certain diarrhea-causing organisms.

SULFASUXIDINE® (succinylsulfathiazole)—an ideal adjunct to neomycin because it is highly effective against Clostridia and certain other neomycin-resistant organisms.

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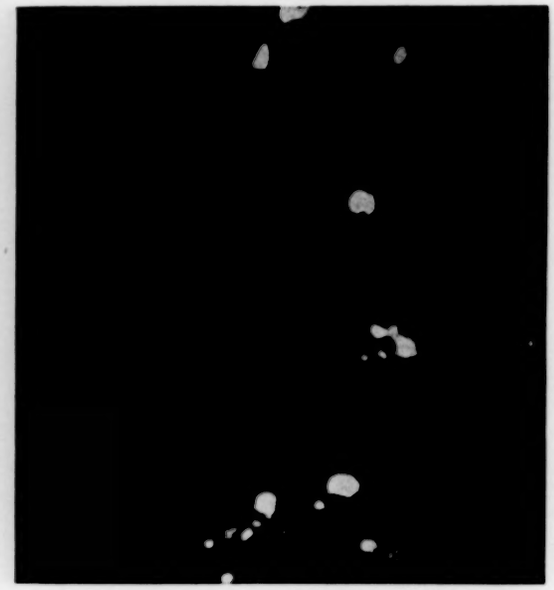
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Clarin* can do this for your postcoronary patients



WITHOUT CLARIN, turbid blood serum five hours after a fat meal: This unretouched dark-field photomicrograph (2500X) shows potentially hazardous fat concentrations circulating in the blood stream of a patient after a standard fat meal.



WITH CLARIN, clear blood serum five hours after a fat meal: After eating a standard fat meal as at left, the same patient has taken one sublingual Clarin tablet. Note marked clearing effect and reduction in massive fat concentrations in this unretouched photomicrograph (2500X).

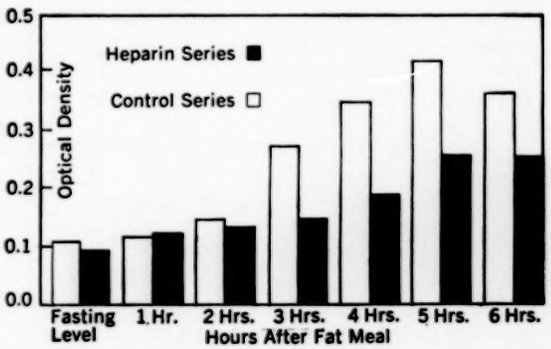
CLARIN is sublingual heparin potassium. One mint-flavored tablet taken after each meal effectively "causes a marked clarification of postprandial lipemic serum."[1] Clarin facilitates the normal physiologic breakdown of fats, with no effects on the blood-clotting mechanism.[1] It therefore provides important benefits for your postcoronary patients.

Indication: For the management of hyperlipemia associated with atherosclerosis.

Dosage: After each meal, hold one tablet under the tongue until dissolved.

Supplied: In bottles of 50 pink, sublingual tablets, each containing 1500 I.U. heparin potassium.

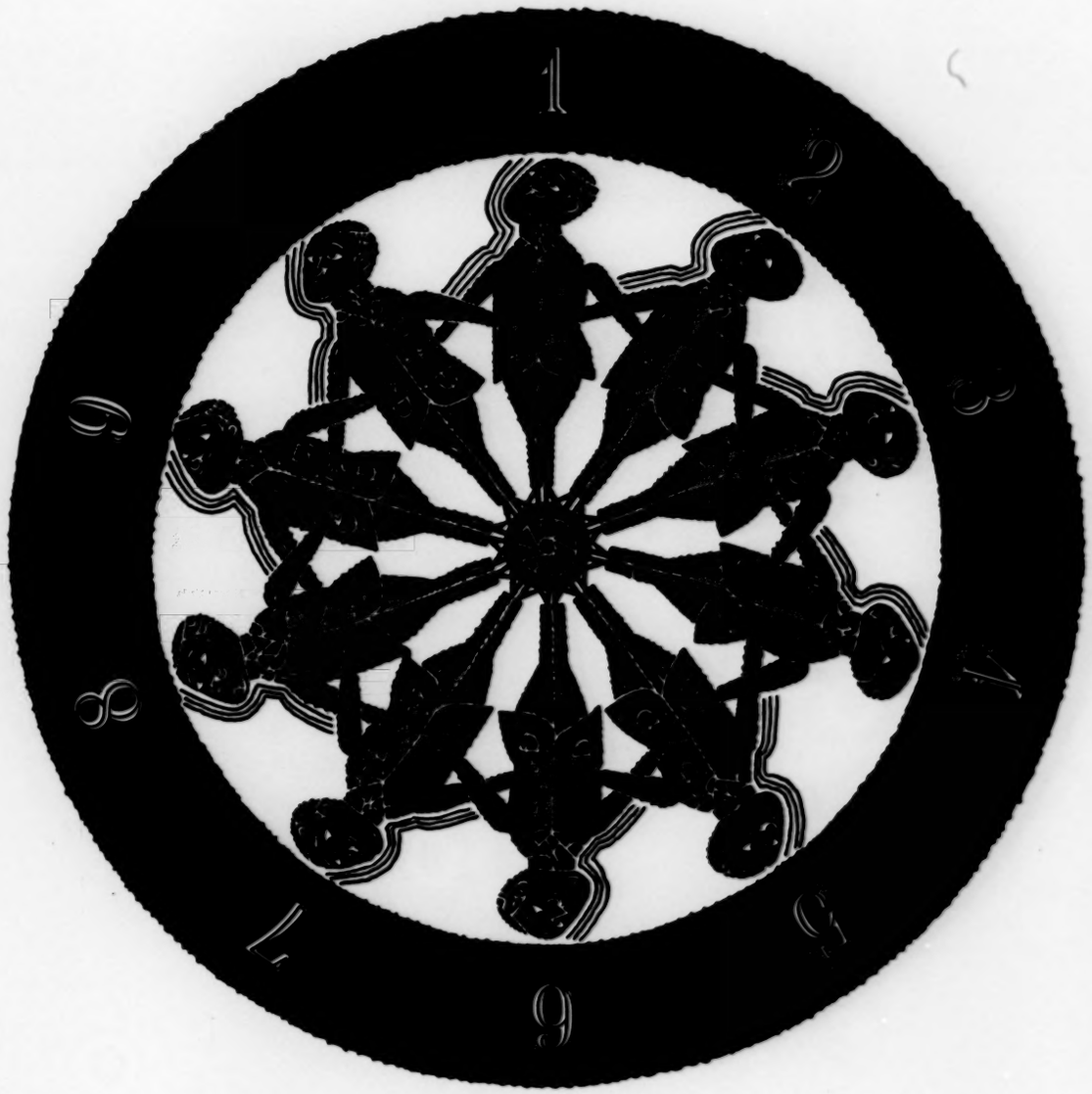
1. Fuller, H. L.: Angiology 9:311 (Oct.) 1958.
2. Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959.



Average serum optical density in 36 patients after fat meal with and without sublingual heparin.[2]

*Registered trade mark. Patent applied for.

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STOPS VERTIGO 9 TIMES OUT OF 10!!

The latest ANTIVERT report confirms earlier findings: ANTIVERT relieves vertigo in 9 out of 10 patients. This combination of meclizine (an outstanding antihistamine for vestibular dysfunction) and nicotinic acid (the drug of choice for prompt vasodilation[1]) "... proved more effective than the use of either drug alone."[2] Out of 50 patients with Meniere's syndrome, only 4 failed to respond to ANTIVERT.[2]

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Supplied: **In bottles of 100 blue-and-white scored tablets. Prescription only.**

References: **1. Menger, H. C.: Clin. Med. *4*:313 (Mar.) 1957. 2. Scal, J. C.: Eye Ear Nose & Throat Month. *38*:738 (Sept.) 1959.**

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a safe, new way to prevent chronic HEADACHE



more effective than other drugs tested for the management of chronic or recurring headache

When SOMA was used prophylactically, "the frequency and/or severity of the attacks were decreased significantly in 73 per cent" with "severe and tenacious" tension headache.* These patients "were selective in that they did not respond satisfactorily to previous medical . . . treatment."[1]

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Therapy	*Per Cent Improved*
SOMA	73
All drugs previously tested (average)†	56
Placebo	50
(*Total cases: 60*)	

†Includes analgesics, antihistamines, CNS stimulants, hormones, sedatives, vasodilators, vasoconstrictors.

FOR PROPHYLAXIS OF CHRONIC HEADACHE: one 350 mg. tablet, q.i.d.; maximal effect is obtained in 3 to 5 days. To treat chronic headache: use a routine analgesic; at the same time start prophylactic treatment with SOMA.

SUPPLY: White, coated 350 mg. tablets, bottles of 50. Also available for pediatric use: orange, 250 mg. capsules, bottles of 50.

1. Friedman, Arnold P.: Clinical Application of Carisoprodol in the Treatment of Chronic Headache. Proceedings of the Symposium on the Pharmacology and Clinical Usefulness of Carisoprodol, Wayne State University Press, Detroit, 1959. p. 115.

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The only drug combining analgesia with muscle relaxation in a single molecule

Literature and samples on request

*SOMA has not been found effective in migraine.

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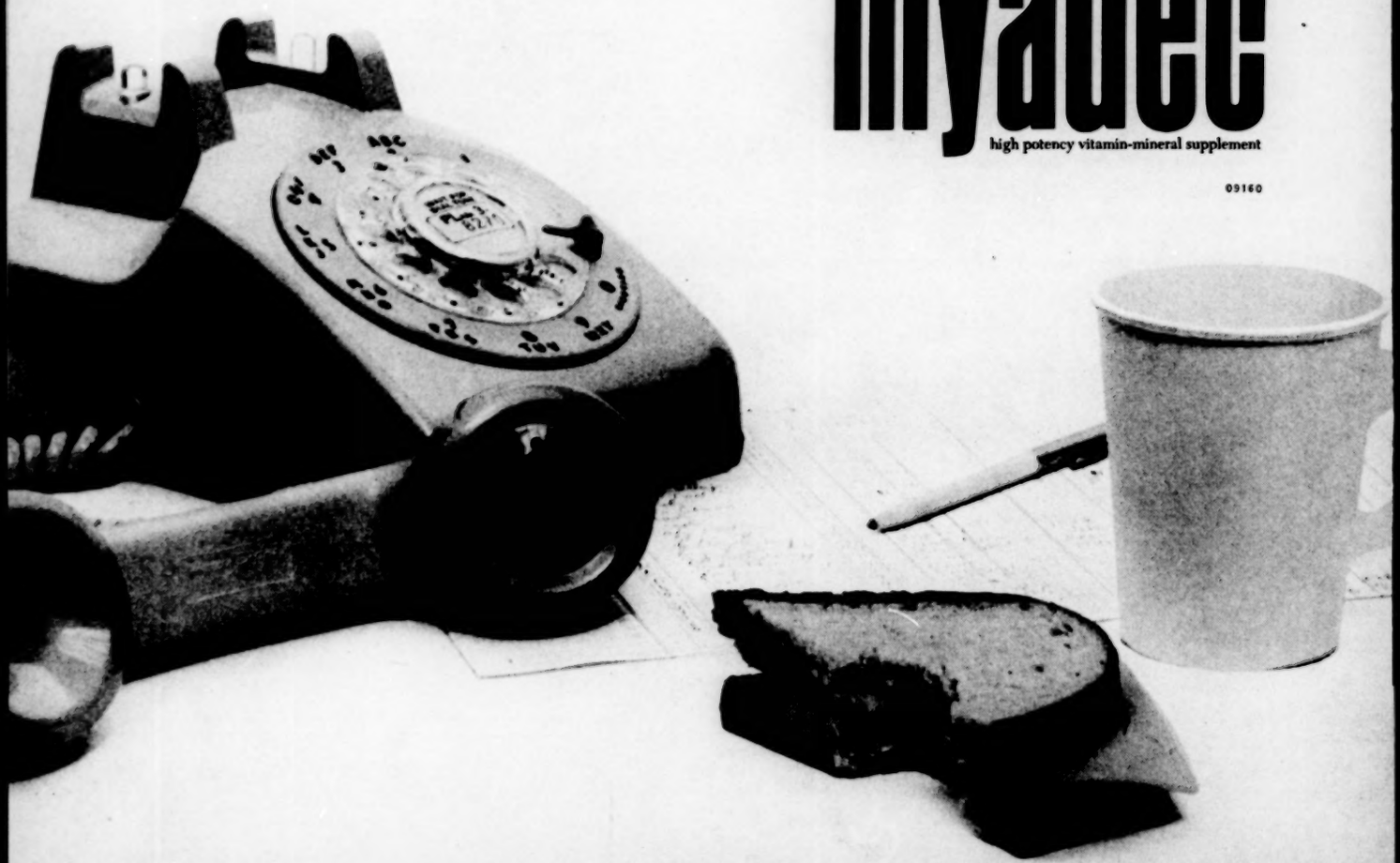
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27 pounds lost in 19 days; ascites and pedal edema reduced with



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Indicated in: congestive heart failure ■ nephrosis and nephritis ■ toxemia of pregnancy ■ premenstrual edema ■ edema of pregnancy ■ steroid-induced edema ■ edema of obesity.

RECORD OF TREATMENT (At a leading New York City hospital. Photos used with permission of the patient.)

Date	3/3	3/4	3/5	3/6	3/7	3/8	3/9	3/10	3/11	3/12	3/13	3/14	3/15	3/16	3/17	3/18	3/19	3/20	3/21	3/22	3/23
Weight (pounds)	178	176	170	169	167	159	158	158	157	153	155	155	156	154	153	154	153	—	—	151	149
Rx	M*		Esidrix 50 mg. b.i.d.																		

*Mercurial diuretic



After 19 Days on Esidrix:
Weight 149 lbs.

H. K., 44 years old, with history of heavy drinking. Previously hospitalized in 1954, with diagnosis of Laennec's cirrhosis. Admitted on 3/3/59, patient complained of swollen abdomen, swelling in both legs and exertional dyspnea.

Findings: Abdomen enlarged in girth with definite fluid wave; liver palpated 4 fingerbreadths below the costal margin; pedal edema (4+). Patient not in acute distress. Blood pressure, 140/80 mm. Hg; pulse, 112/min.; respiration, 20/min.

Treatment: Mercurial diuretic on 3/3 and 3/4, followed by Esidrix, 50 mg. b.i.d., from 3/5 to 3/23 when patient signed out of hospital. Esidrix induced copious diuresis resulting in almost complete disappearance of edema.

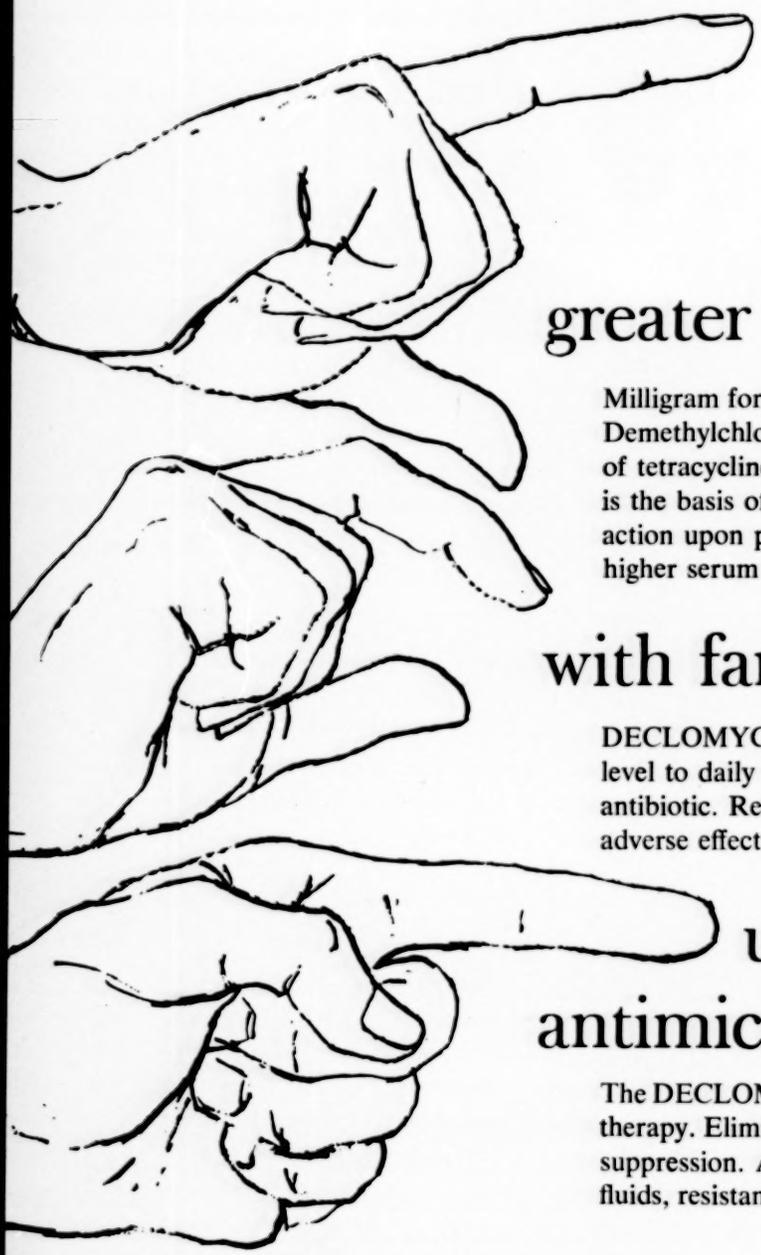
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DECLOMYCIN demonstrates the highest ratio of prolonged activity level to daily milligram intake of any known broad-spectrum antibiotic. Reduction of antibiotic intake reduces likelihood of adverse effect on intestinal mucosa or interaction with contents.

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*Hirsch, H. A., and Finland, M.: *New England J. Med.* 260:1099 (May 28) 1959.

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DECLOMYCIN maintains activity for one to two days after discontinuance of dosage. Features unusual security against resurgence of primary infection or secondary bacterial invasion—two factors often resembling a "resistance problem"—enhancing the traditional advantages of tetracycline . . . for greater physician-patient benefit

in the distinctive dry-filled, duotone capsule

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DECLOMYCIN Capsules, 150 mg., bottles of 16 and 100. Adult dosage: 1 capsule four times daily.

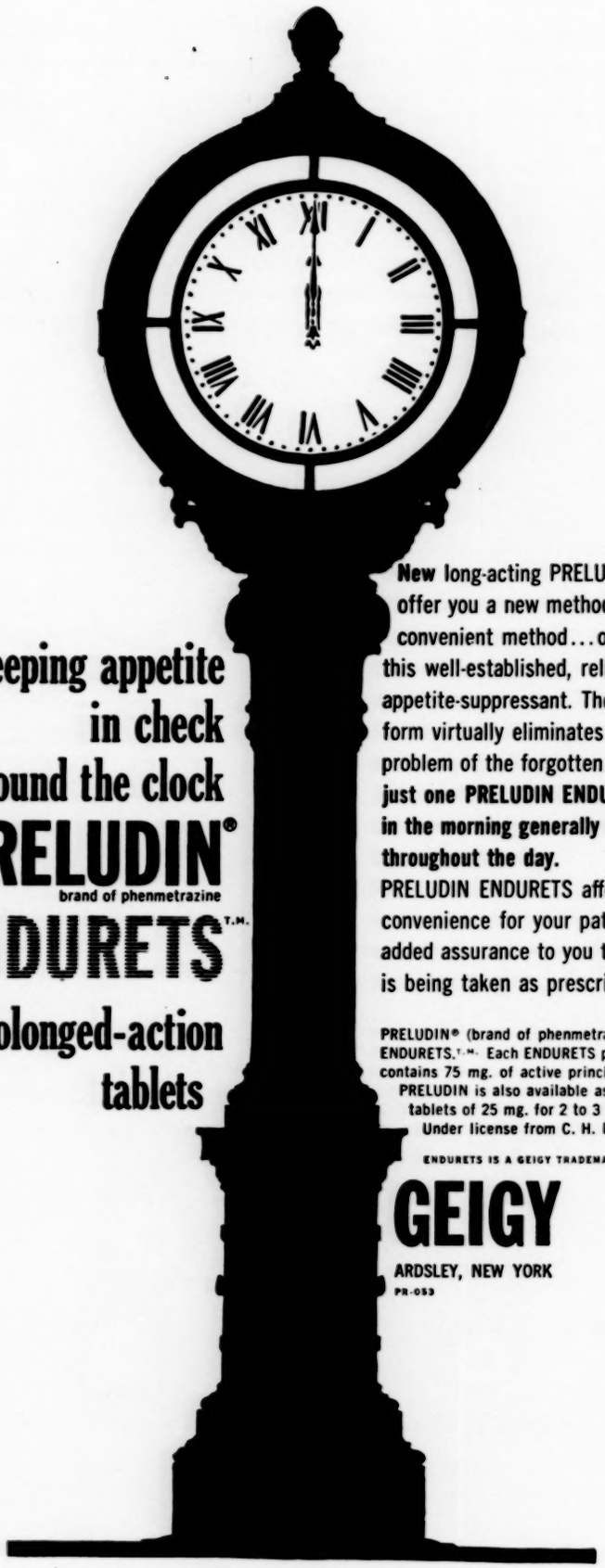
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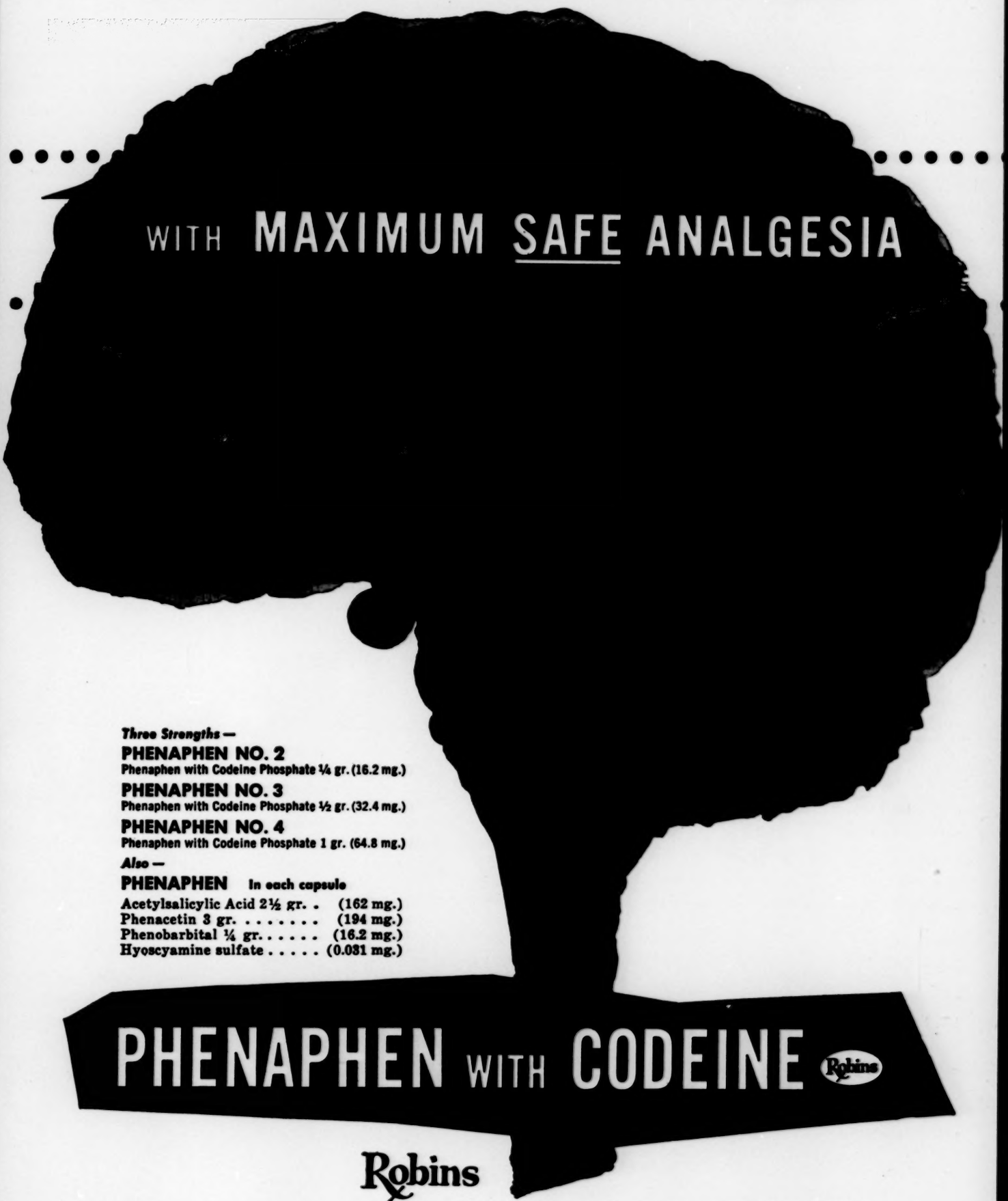
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Acetylsalicylic Acid 2½ gr. . (162 mg.)
Phenacetin 3 gr. . . . . (194 mg.)
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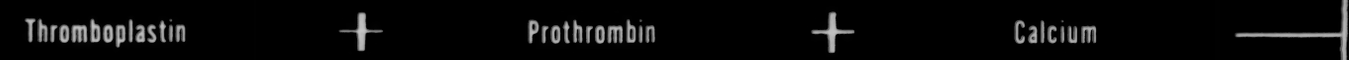
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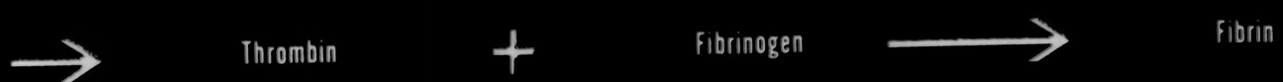
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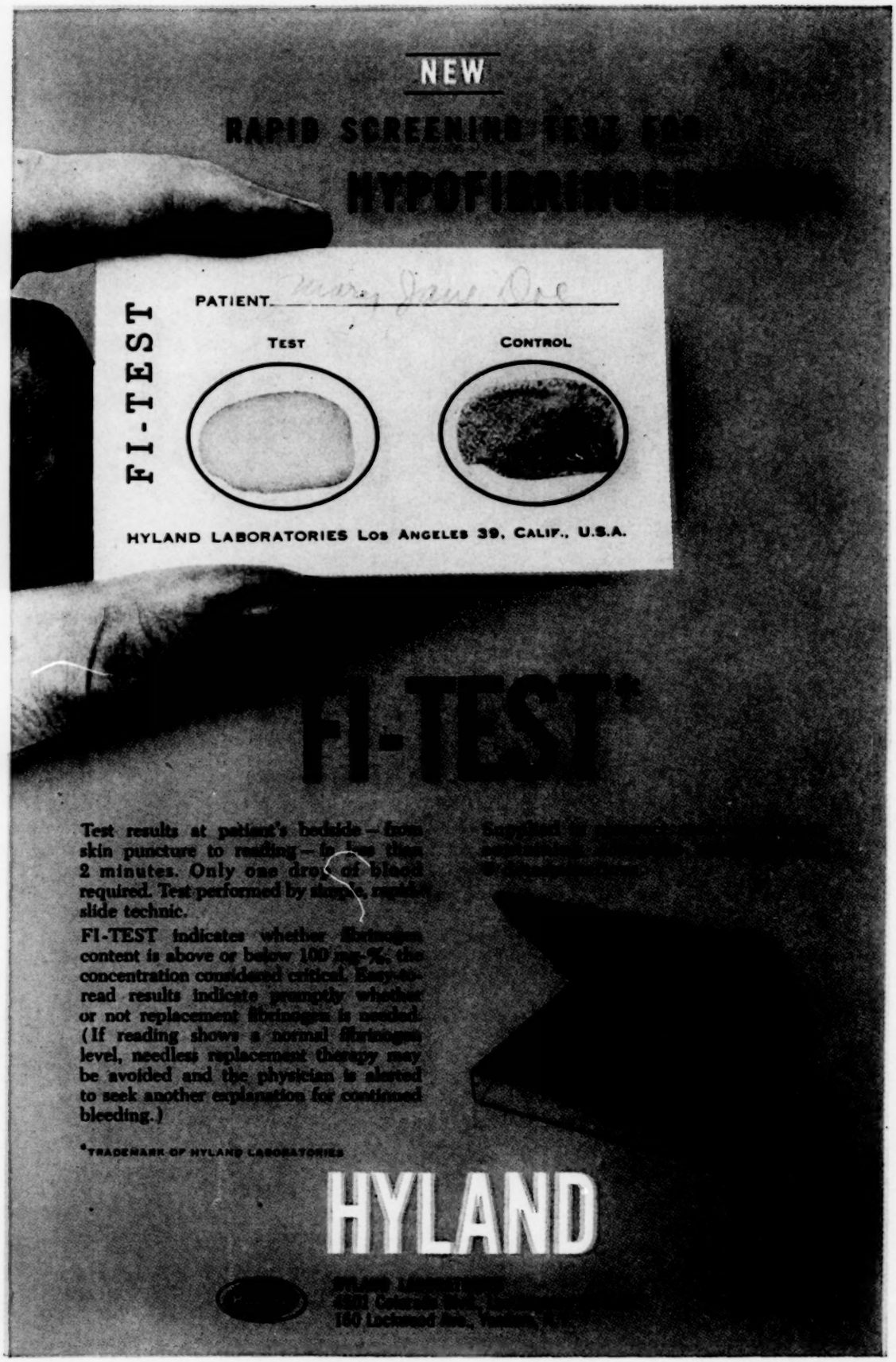


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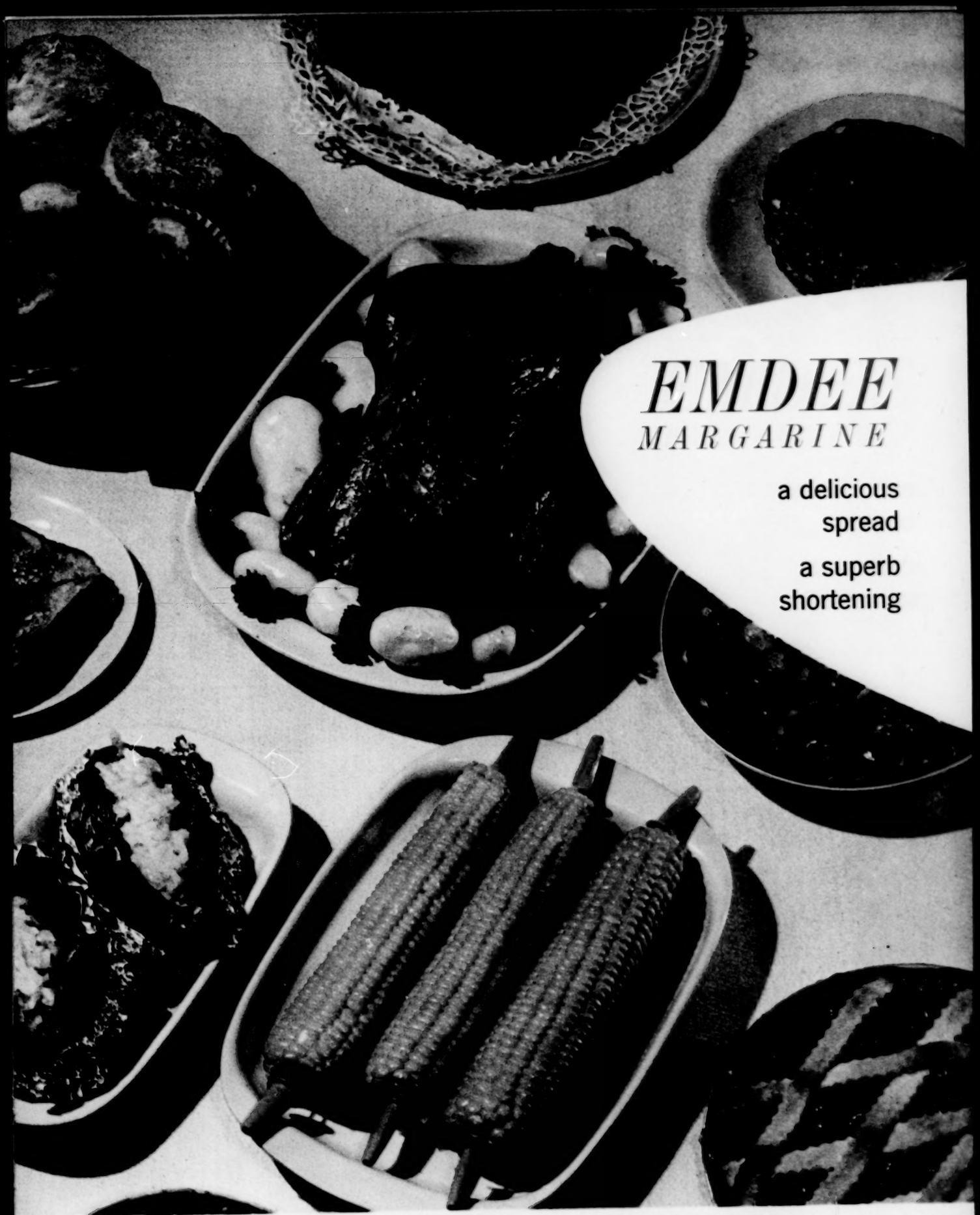
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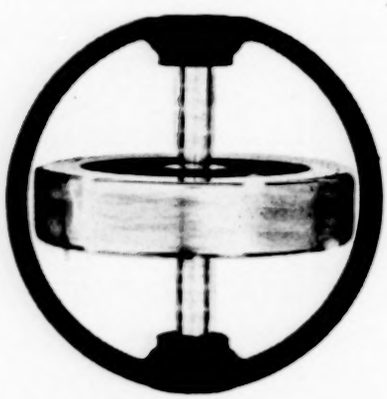
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References: 1. Feinberg, S. M.; Feinberg, A. R., and Fisherman, E. W.: *J.A.M.A.* 167:58 (May 3) 1958. 2. Epstein, J. I., and Sherwood, H.: *Conn. Med.* 22:822 (Dec.) 1958. 3. Friedlaender, S., and Friedlaender, A. S.: *Antibiotic Med. & Clin. Ther.* 5:315 (May) 1958. 4. Segal, M. S., and Duvenci, J.: *Bull. Tufts N.E. Medical Center* 4:71 (April-June) 1958. 5. Segal, M. S.: Report to the A.M.A. Council on Drugs, *J.A.M.A.* 169: 1063 (March 7) 1958. 6. Hartung, E. F.: *J. Florida Acad. Gen. Practice* 8:18, 1957. 7. Rein, C. R.; Fleischwager, R., and Rosenthal, A. L.: *J.A.M.A.* 165:1821 (Dec. 7) 1957. 8. McGavack, T. H.: *Clin. Med.* (June) 1959. 9. Freyberg, R. H.; Berntsen, C. A., and Hellman, L.: *Arthritis & Rheumatism* 1:215 (June) 1958. 10. Hartung, E. F.: *J.A.M.A.* 167:973 (June 21) 1958. 11. Zuckner, J.; Ramsey, R. H.; Caciolo, C., and Gantner, G. E.: *Ann. Rheumat. Dis.* 17:398 (Dec.) 1958. 12. Appel, B.; Tye, M. J., and Leibsohn, E.: *Antibiotic Med. & Clin. Ther.* 5:716 (Dec.) 1958. 13. Kalz, F.: *Canad. M.A.J.* 79:400 (Sept.) 1958. 14. Mullins, J. F., and Wilson, C. J.: *Texas J. Med.* 54:648 (Sept.) 1958. 15. Shelley, W. B.; Harun, J. S., and Pillsbury, D. M.: *J.A.M.A.* 167:959 (June 21) 1958. 16. DuBois, E. L.: *J.A.M.A.* 167:1590 (July 26) 1958. 17. McGavack, T. H.; Kao, K. T.; Leake, D. A.; Bauer, H. G., and Berger, H. E.: *Am. J. M. Sc.* 236:720 (Dec.) 1958. 18. Council on Drugs: *J.A.M.A.* 169:257 (January) 1959.

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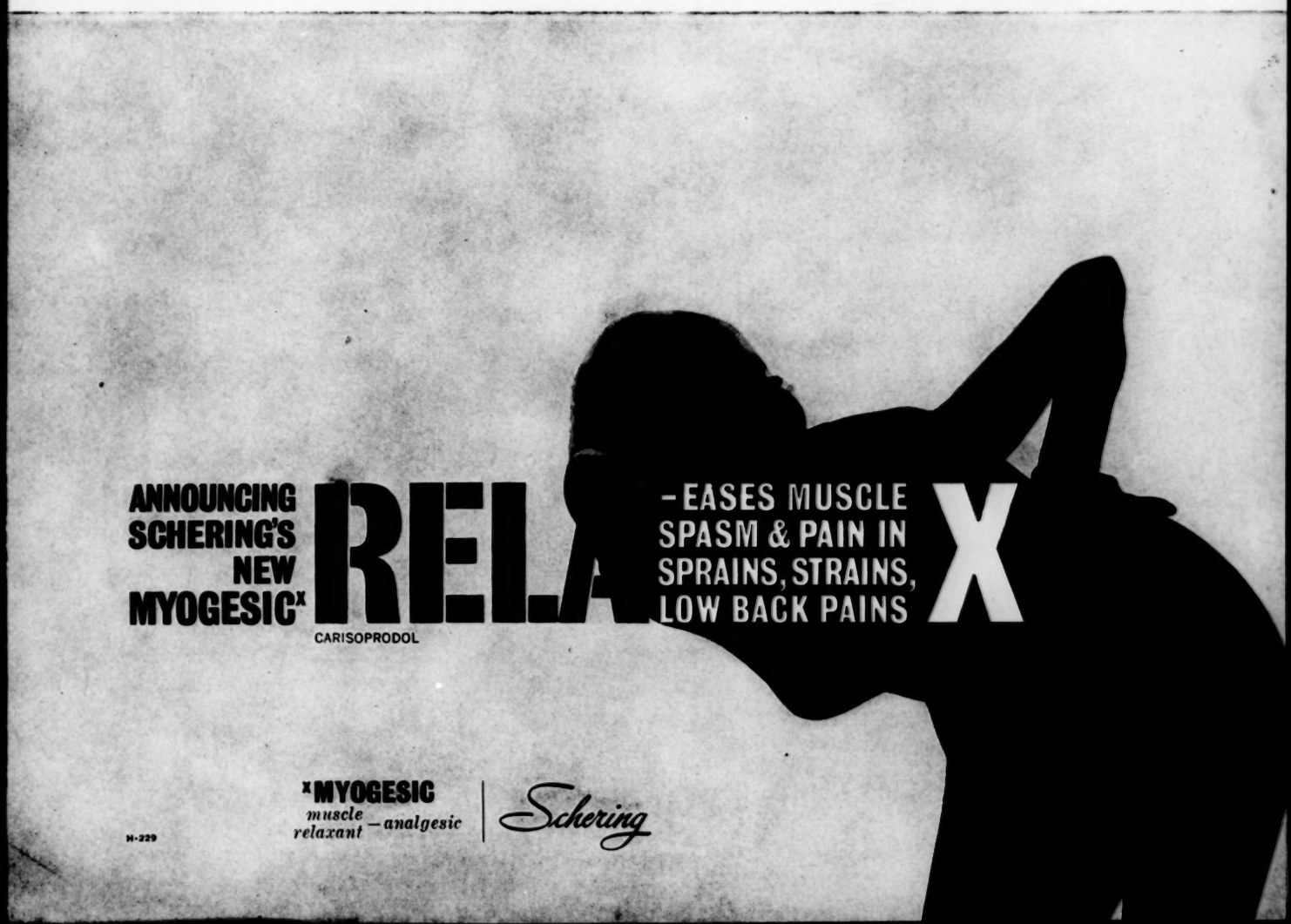
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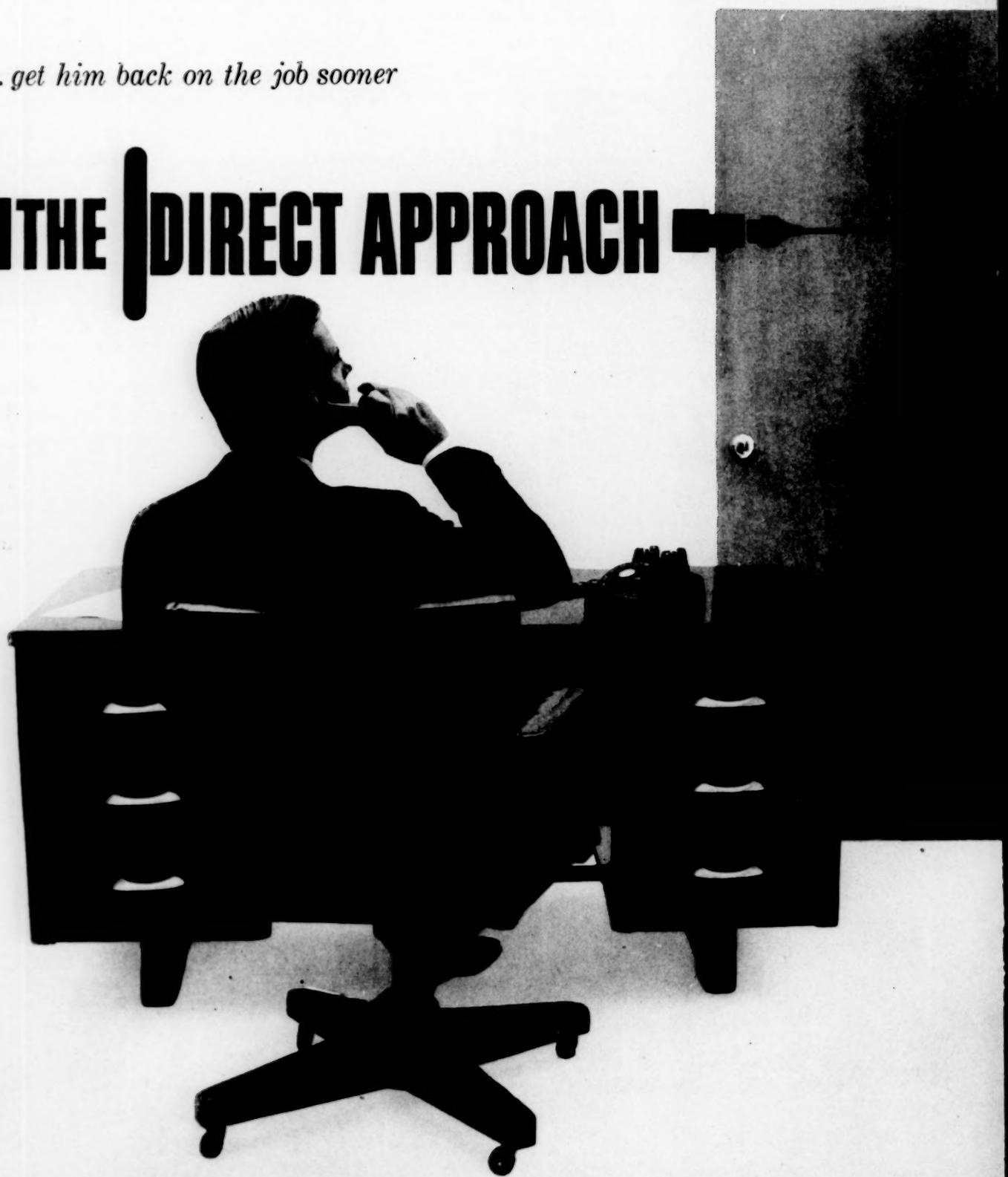
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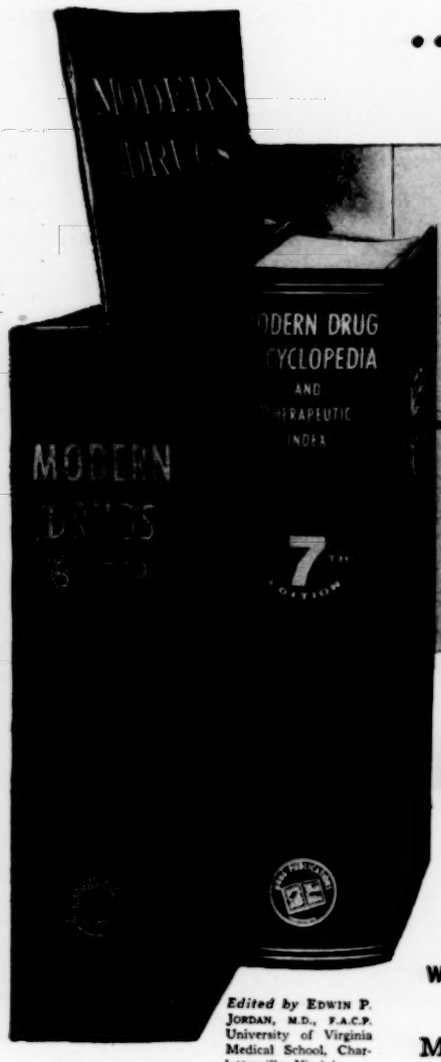
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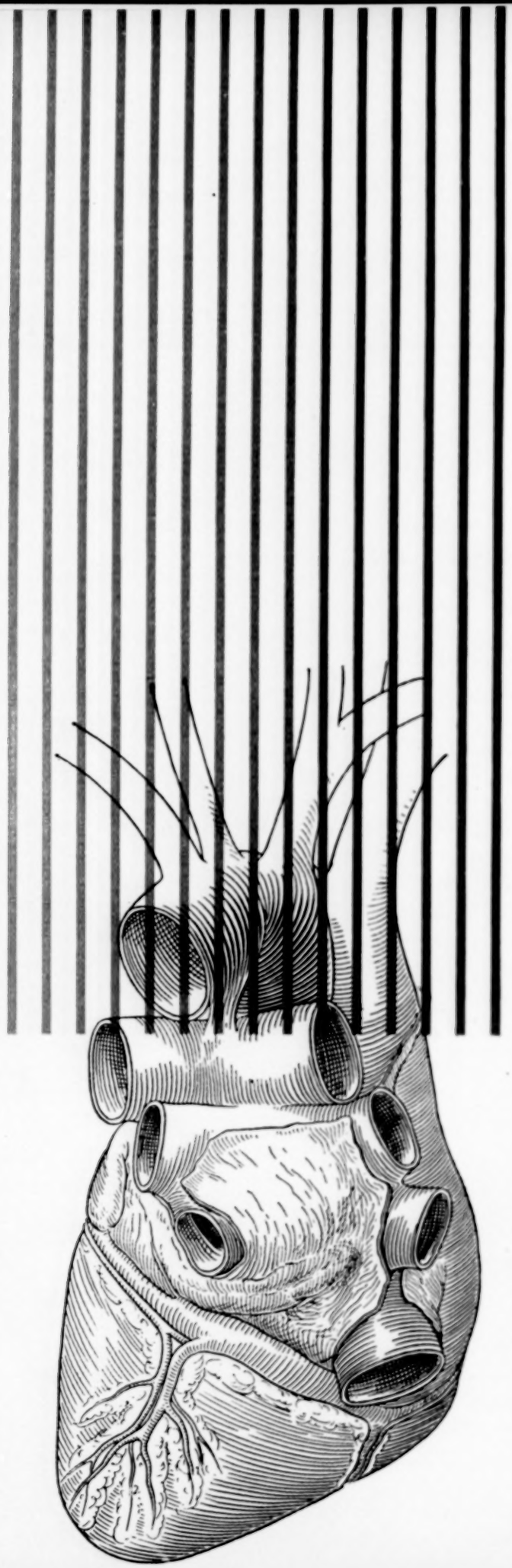
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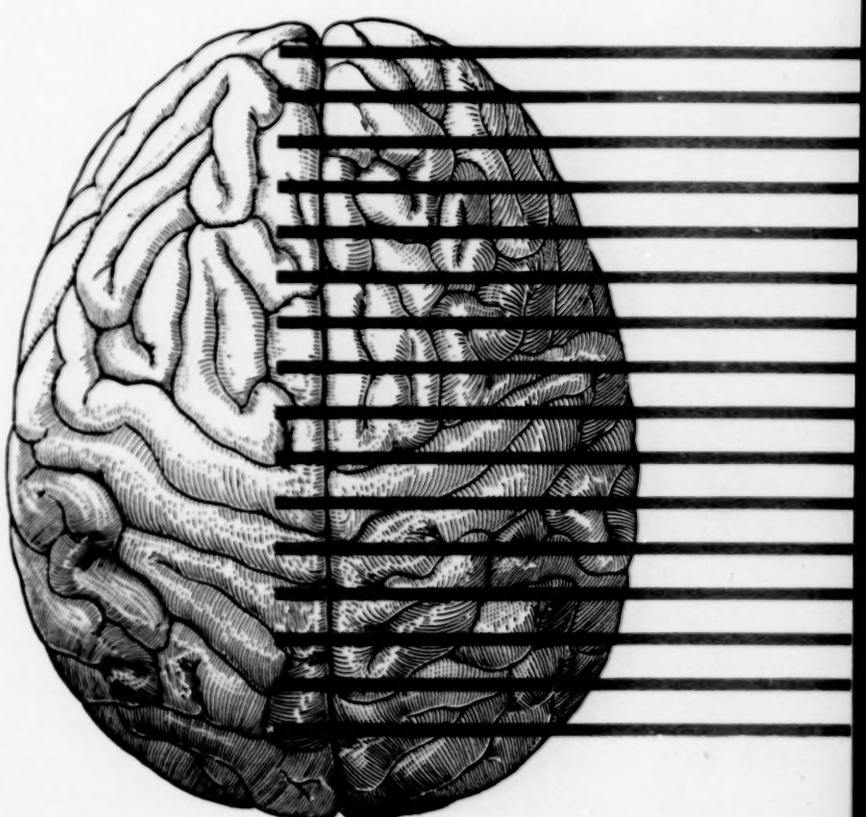
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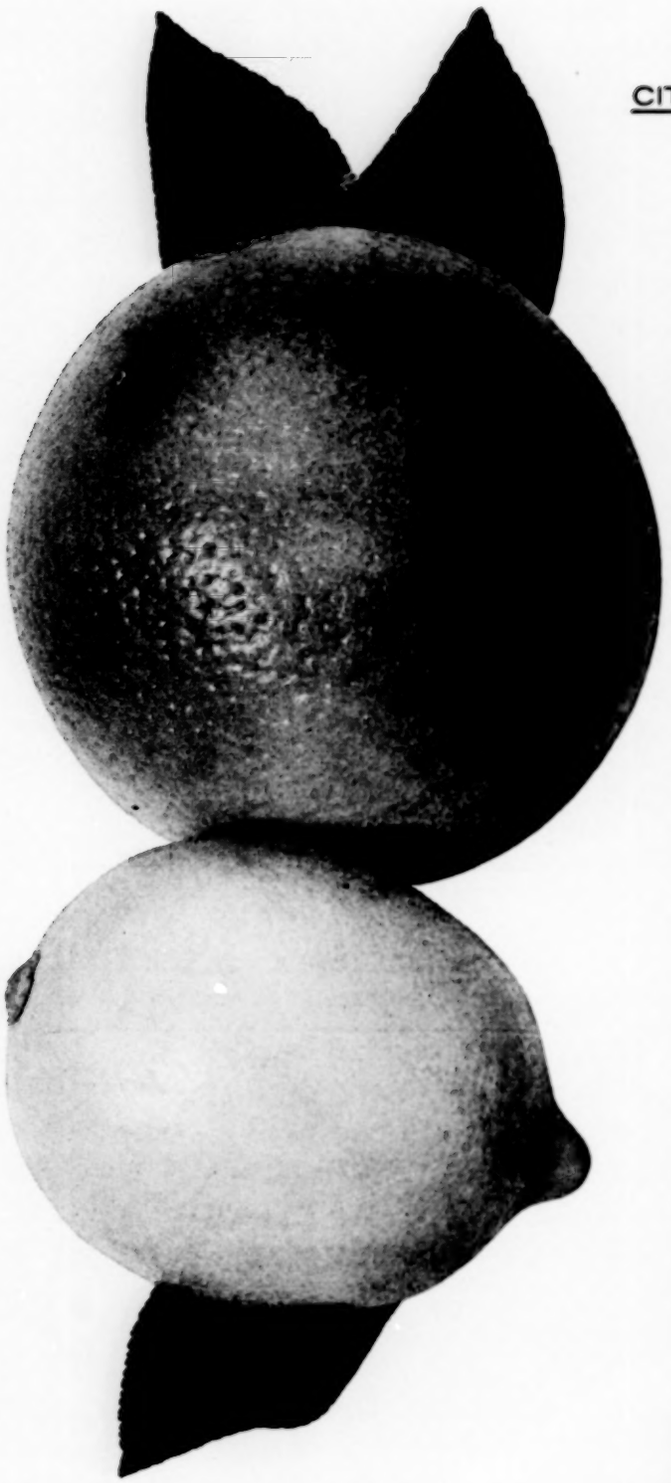
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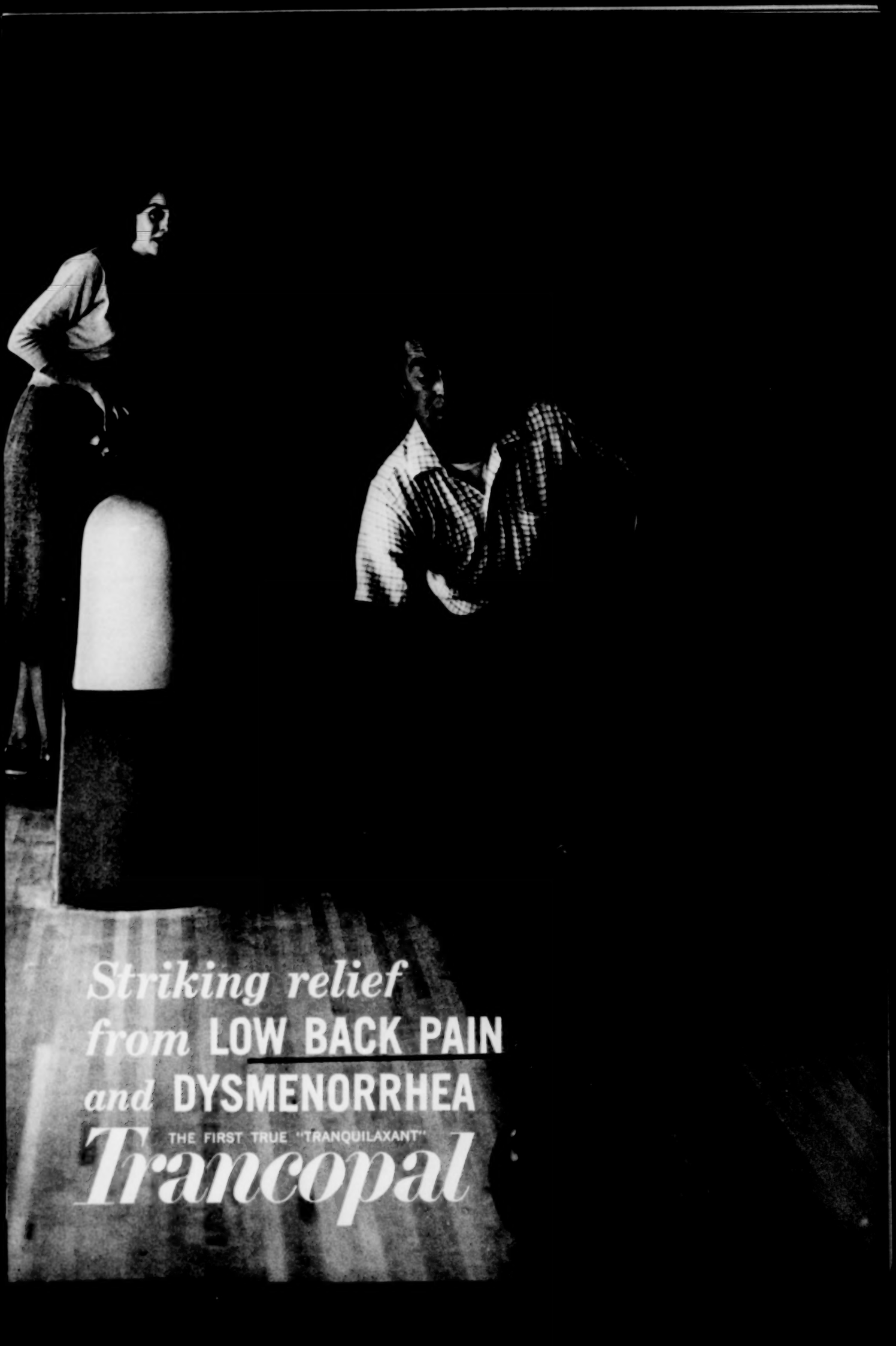
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†Analysis of clinical reports.

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MSD **MERCK SHARP & DOHME**
Division of Merck & Co., Inc., Philadelphia 1, Pa.


Striking relief
from LOW BACK PAIN
and DYSMENORRHEA
THE FIRST TRUE "TRANQUILAXANT"
Trancopal

Here is what you can expect when you prescribe

for dysmenorrhea

and premenstrual tension

Case Profile*

A 28-year-old married woman, a secretary in a booking agency, complained of severe and consistent pain and cramps in the abdomen during her menstrual periods. Psychologically, she described the first two days as "climbing the walls." Menarche occurred at age 13. She has a regular twenty-eight day menstrual cycle and a four day menstrual period.

Trancopal was given in a dose of 100 mg. four times a day for the first two days of the four day period. In addition to the relief of the dysmenorrhea she also noticed disappearance of a "bloated feeling" that had previously annoyed her. She has now been treated with Trancopal for one and one-half years with excellent results. Other medication, such as codeine or aspirin with codeine, had relieved the pain, but the patient had had to stay home. Because her father is a physician, many commercial preparations had been tried prior to Trancopal, but no success had been achieved.

Before taking Trancopal this patient missed one day of work every month. For the past year and a half she has not missed a day because of dysmenorrhea.



THE FIRST TRUE "TRANQUILAXANT"

Trancopal®

for low back pain



Case Profile*

A 42-year-old truck driver and mover injured his back while moving a piano. The pain radiated from the sacral region down to the region of the Achilles tendon on the right side. X-rays for ruptured disc revealed nothing pertinent. The day of the injury he was given Trancopal immediately after the physical examination. Although 100 to 200 mg. three times a day were prescribed, the patient on his own responsibility increased the dosage of Trancopal to 400 mg. three times a day. This dosage was continued for three days and then gradually reduced over a ten day period. During this time, the patient continued to drive his truck. The muscle spasm was completely controlled and no apparent side effects were noted.

For the past six months, the patient has continued to take Trancopal 100 to 200 mg. as needed for muscle spasm, particularly during strenuous days.

**Clinical Reports on file at the Department of Medical Research, Winthrop Laboratories.*

Turn page for complete listings of Indications and Dosage.

THE FIRST TRUE "TRANQUILAXANT"

Trancopal

potent MUSCLE RELAXANT

effective TRANQUILIZER

- In musculoskeletal disorders, effective in 91 per cent of patients.[1]
- In anxiety and tension states, effective in 89 per cent of patients.[1]
- Low incidence of side effects (2.3 per cent of patients). Blood pressure, pulse rate, respiration and digestive processes are unaffected by therapeutic dosage. It does not affect the hematopoietic system or liver and kidney function.
- No gastric irritation. Can be taken before meals.
- No clouding of consciousness, no euphoria or depression.

Indications [1-6]

Musculoskeletal:

- Low back pain (lumbago, etc.)
- Neck pain (torticollis)
- Bursitis
- Rheumatoid arthritis
- Osteoarthritis
- Disc syndrome
- Fibrositis
- Ankle sprain, tennis elbow
- Myositis
- Postoperative muscle spasm

Psychogenic:

- Anxiety and tension states
- Dysmenorrhea
- Premenstrual tension
- Asthma
- Angina pectoris
- Alcoholism

Now available in two strengths:



Trancopal Caplets®,
100 mg. (peach colored, scored), bottles of 100.

NEW STRENGTH ▶



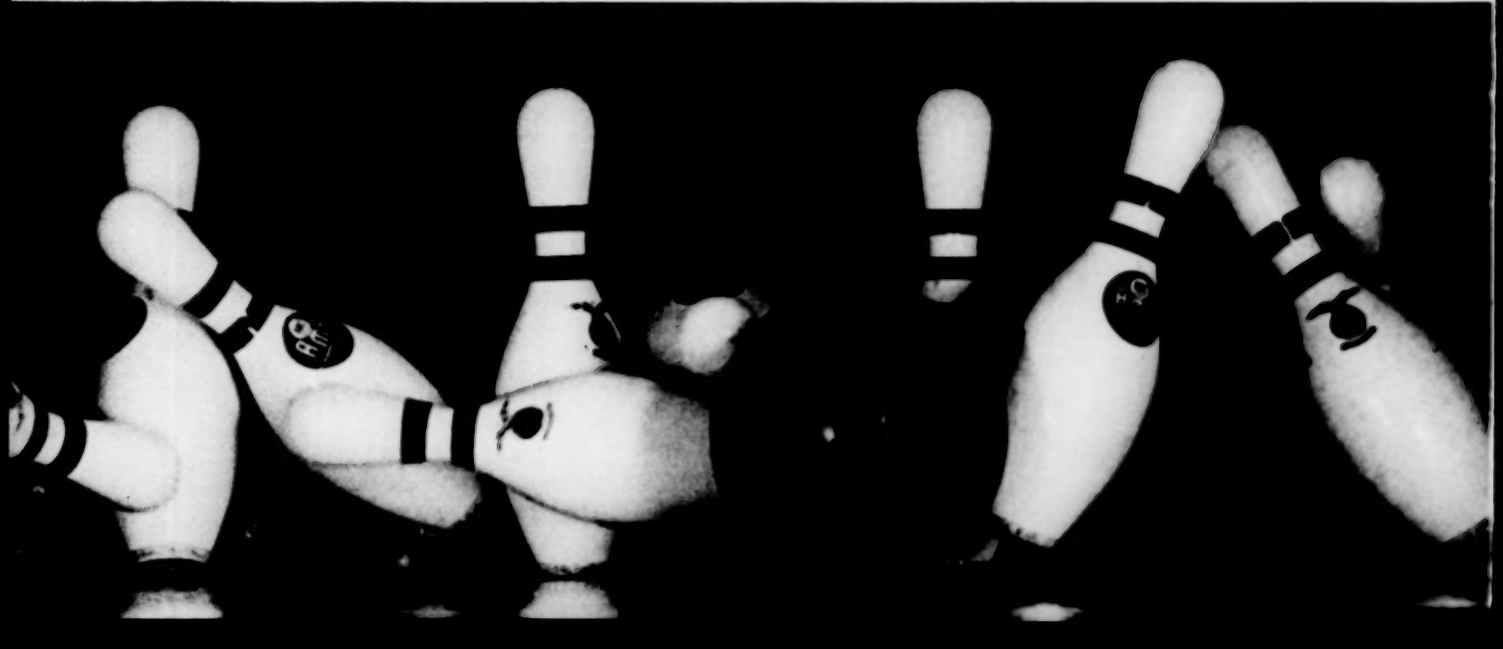
Trancopal Caplets,
200 mg. (green colored, scored), bottles of 100.

Dosage: Adults, 100 or 200 mg. orally three or four times daily. Relief of symptoms occurs in from fifteen to thirty minutes and lasts from four to six hours.

Winthrop LABORATORIES
New York 18, N. Y.

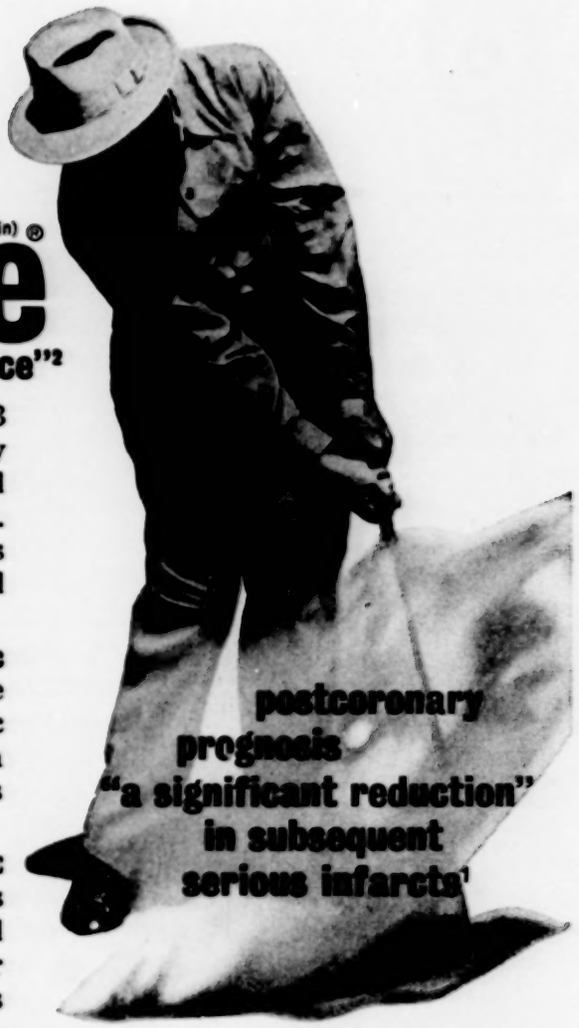
References: 1. Collective Study, Department of Medical Research, Winthrop Laboratories. 2. Lichtman, A. L.: New developments in muscle relaxant therapy, *Kentucky Acad. Gen. Pract. J.* 4:28, Oct., 1958. 3. Lichtman, A. L.: Relief of muscle spasm with a new central muscle relaxant, chlormezanone (Trancopal), Scientific Exhibit, Meeting of the International College of Surgeons, Miami Beach, Fla., Jan. 4-7, 1959. 4. Ganz, S. E.: Clinical evaluation of a new muscle relaxant (chlormethazanone), *J. Indiana M. A.* 52:1134, July, 1959. 5. Mullin, W. G., and Epifano, Leonard: Chlormezanone, a tranquilizing agent with potent skeletal muscle relaxant properties, *Am. Pract. Digest Treat.* 10:1743, Oct., 1959. 6. Shanaphy, J. F.: Chlormezanone (Trancopal) in the treatment of dysmenorrhea: a preliminary report, *Current Therap. Res.* 1:59, Oct., 1959.

Trancopal (brand of chlormezanone) and Caplets, trademarks reg. U.S. Pat. Off. 1408M Printed in U.S.A.



Danilone (Phenindione, Schieffelin) ®

"the anticoagulant drug of choice"[2]



When DANILONE was administered to 33 postmyocardial infarct patients, only two thromboembolic episodes occurred in two patients in 565 patient-months. Five such episodes in 50 patient-months occurred in four patients who had stopped taking anticoagulants.[3]

"twice as fast in reaching therapeutic levels"[4] In 117 patients, the average time DANILONE required to attain therapeutic levels was less than 36 hours.[4] With bishydroxycoumarin, two to four days are required for equal effect.[5]

"a greater degree of control"[6] DANILONE held prothrombin activity in 200 patients to between 5 and 10 per cent of normal "with greater facility" than in another series where bishydroxycoumarin was used.[6] Generally, most satisfactory control can be obtained by dividing the dosage schedule into two 12-hour intervals.[3,6]

"a reputation for safety"[7] DANILONE, unlike the coumarin derivatives, has a short recovery period and no cumulative action.[5,8,9] As a result, DANILONE "... can be administered with reasonable safety in the presence of many conditions which would contraindicate the use of Dicoumarol."[6]

"a lack of toxic reactions"[3] Because of its extremely low incidence of toxicity,[2,4,9] and "... the apparent safety factor of a wide spread between therapeutic and toxic dose, it is felt that phenyldanedione [phenindione] is the anticoagulant drug of choice."[2]

"inexpensive"[5] DANILONE is the least expensive anticoagulant available today. Maintenance cost is as little as three cents a day. In addition, its stability of effect permits fewer prothrombin-time tests,[9] saving the patient additional costs.

Samples and literature available on request.

SUPPLIED: 50 mg. scored tablets. Bottles of 100 and 1,000.

References: 1. Pickering, G., et al.: Brit. M. J. 1:803 (Mar. 28) 1959. 2. McCabe, E. S., and Fittipoldi, J., Jr.: Am. Pract. & Digest Treat. 4:765, 1953. 3. Drinan, F. W., et al.: Am. Heart J. 53:284, 1957. 4. Harper, B. F., and Johnson, R.: J.M.A. Georgia 45:149, 1956. 5. Wood, J. E.; Beckwith, J. R., and Camp, J. L., III: J.A.M.A. 159:635 (Oct. 15) 1955. 6. Sise, H. S.; Maloney, W. C., and Guttas, C. G.: Am. Heart J. 53:132, 1957. 7. Newcomb, T. F.: New England J. Med. 260:545 (Mar. 12) 1959. 8. O'Connor, W. R.; Thompson, C. E., and Baker, L. A.: Quart. Bull. Northwestern Univ. M. School 26:193 (Fall) 1952. 9. Toohey, M.: Brit. M. J. 1:650 (Mar. 21) 1953.

Schieffelin

Schieffelin & Co. / Since 1794 Pharmaceutical Laboratories Division, New York 3

New Enzyme-controlled antifungal therapy to meet the growing challenge of **Monilial Vaginitis**

IN PREGNANCY / IN DIABETES / AFTER ANTIBIOTIC THERAPY–Today, monilial vaginitis is estimated to be a problem in at least 33 per cent of pregnant women and about 10 per cent of nonpregnant females[1]—a rapidly increasing incidence attributed partly to the widespread use of antibiotics.

"Vanay" Vaginal Cream broadens the scope of specific therapy: (1) "Vanay" insures a continuous therapeutic fungistatic effect without danger of local reaction; (2) in addition, "Vanay" restores and maintains a physiologic pH and normal vaginal flora—reducing risk of reinfection.

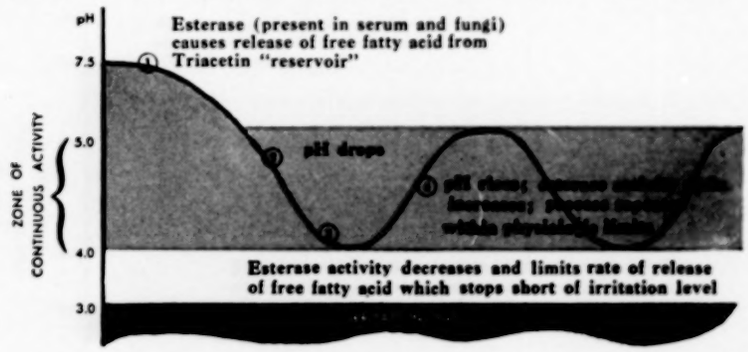
Effective response: Treatment was notably effective in moniliasis, as confirmed by symptomatic relief and post-treatment smears, Assali reports.[2] Marked clinical improvement was also noted in 154 of 206 patients, and in some cases symptoms subsided within a week of therapy.[3]

Other advantages: No monilial resistance demonstrated[4] / prolonged duration of activity[4] / nonsensitizing / nonirritating / nonstaining / odorless.

"VANAY" Vaginal Cream

BRAND OF TRIACETIN IN NONLIQUEFYING BASE

UNIQUE ENZYME-CONTROLLED FUNGISTASIS WITHOUT IRRITATION[5,6]



Indications: specific in monilial vaginitis...adjunctive in trichomoniasis . . . also valuable in nonspecific vaginitis where an acid pH must be restored and maintained.

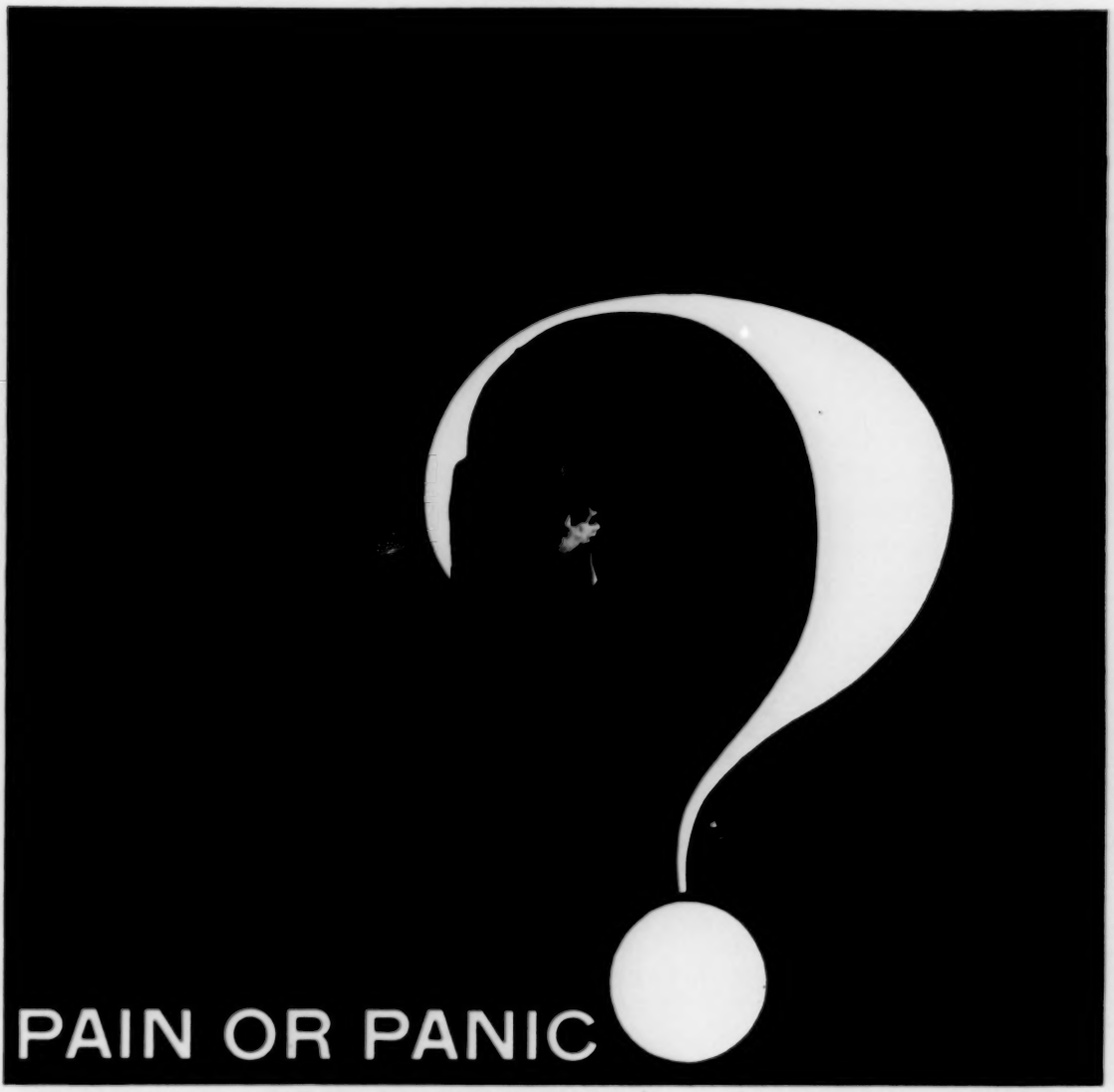
Usual Dosage: 2 to 4 grams daily.

Supplied: No. 204-250 mg. Glyceryl triacetate per gram in a nonliquefying base. Combination package: 1½ oz. tube with 15 disposable applicators.

References: 1. Idson, B.: Drug & Cosmetic Industry *84*:30 (Jan.) 1959. 2. Assali, N. S.: Personal communication. 3. Combined results of 18 clinical investigators, Medical Records, Ayerst Laboratories. 4. Kubista, R. A., and Derse, P. H.: Antibiotics & Chemotherapy, to be published. 5. Knight, S. G.: J. Invest. Dermat. *28*:363 (May) 1957. 6. Knight, S. G.: Antibiotics & Chemotherapy 7:172 (Apr.) 1957.

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Your angina patient hardly knows where one leaves off and the other begins. What he does recognize is the relief he gets from **both** when you prescribe CARTRAX.

FOR ANGINAL PAIN

PETN (pentaerythritol tetranitrate) is ". . . the most effective drug currently available for prolonged prophylactic treatment of angina pectoris."[1]

FOR CARDIAC PANIC

"I favor ATARAX [as the tranquilizer for the anxious cardiac] . . . because there is an absence of side effects with this drug, and also because in cardiacs who are troubled with ectopic beats, ATARAX has a quinidine-like action."[2]

CARTRAX®

PETN + ATARAX®*

Dosage: Begin with 1 to 2 yellow CARTRAX "10" tablets (10 mg. PETN plus 10 mg. ATARAX) 3 to 4 times daily. When indicated, this may be increased by switching to pink CARTRAX "20" tablets (20 mg. PETN plus 10 mg. ATARAX). For convenience, write "CARTRAX 10" or "CARTRAX 20." **Supplied:** In bottles of 100. Prescription only.

*brand of hydroxyzine

References: 1. Russek, H. I.: Postgrad. Med. 19:562 (June) 1956. 2. Russek, H. I.: Presented at the Symposium on the Management of Cardiovascular Problems of the Aged, Dade County Medical Association, Miami Beach, April 12, 1958.

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Science for the World's Well-Being

In hypoprothrombinemia

KONAKION

Rapid action	rate of absorption faster than menadione or derivatives... more potent and lasting effects.
Wide margin of safety	substantially safer than vitamin-K analogues—no kernicterus reported.
Versatility of administration	capsules for oral use...fine aqueous dispersion for parenteral administration.
Compatibility	unlike vitamin-K analogues or similar products, the parenteral form of Konakion is a fine aqueous dispersion compatible with most I.V. vehicles.
Low dosage forms	no excess, no waste—packaged for economical one-time use.

Prophylactically and therapeutically, Konakion is indicated in obstetrics to prevent or control neonatal hemorrhage, to minimize excessive bleeding in surgery, to offset anticoagulant overdosage, and whenever vitamin-K utilization is impaired.

KONAKION®—brand of vitamin K_1
ROCHE® Capsules—5 mg; Ampuls—**1 mg/0.5 cc; 10 mg/1 cc; 25 mg/2.5 cc**



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consistently successful

in a wide variety of infectious diseases encountered in daily practice. More than 120 published clinical reports attest to the superiority and effectiveness of oleandomycin-tetracycline.

Cosa-Signemycin®

glucosamine-potentiated tetracycline with triacetyloleandomycin

antibiotic of choice when sensitivity testing is difficult or impractical.

THE HOUSE-CALL ANTIBIOTIC



available as:

Capsules	Oral Suspension *raspberry-flavored*	Pediatric Drops
125 mg. 250 mg.	2 oz. bottle, 125 mg. per teaspoonful (5 cc.)	10 cc. bottle (with calibrated dropper), 5 mg. per drop (100 mg. per cc.)

Each 250 mg. of Cosa-Signemycin contains: glucosamine-potentiated tetracycline—167 mg., triacetyloleandomycin—83 mg.

Bibliography and professional information booklet on* COSA-SIGNEMYCIN *available on request.

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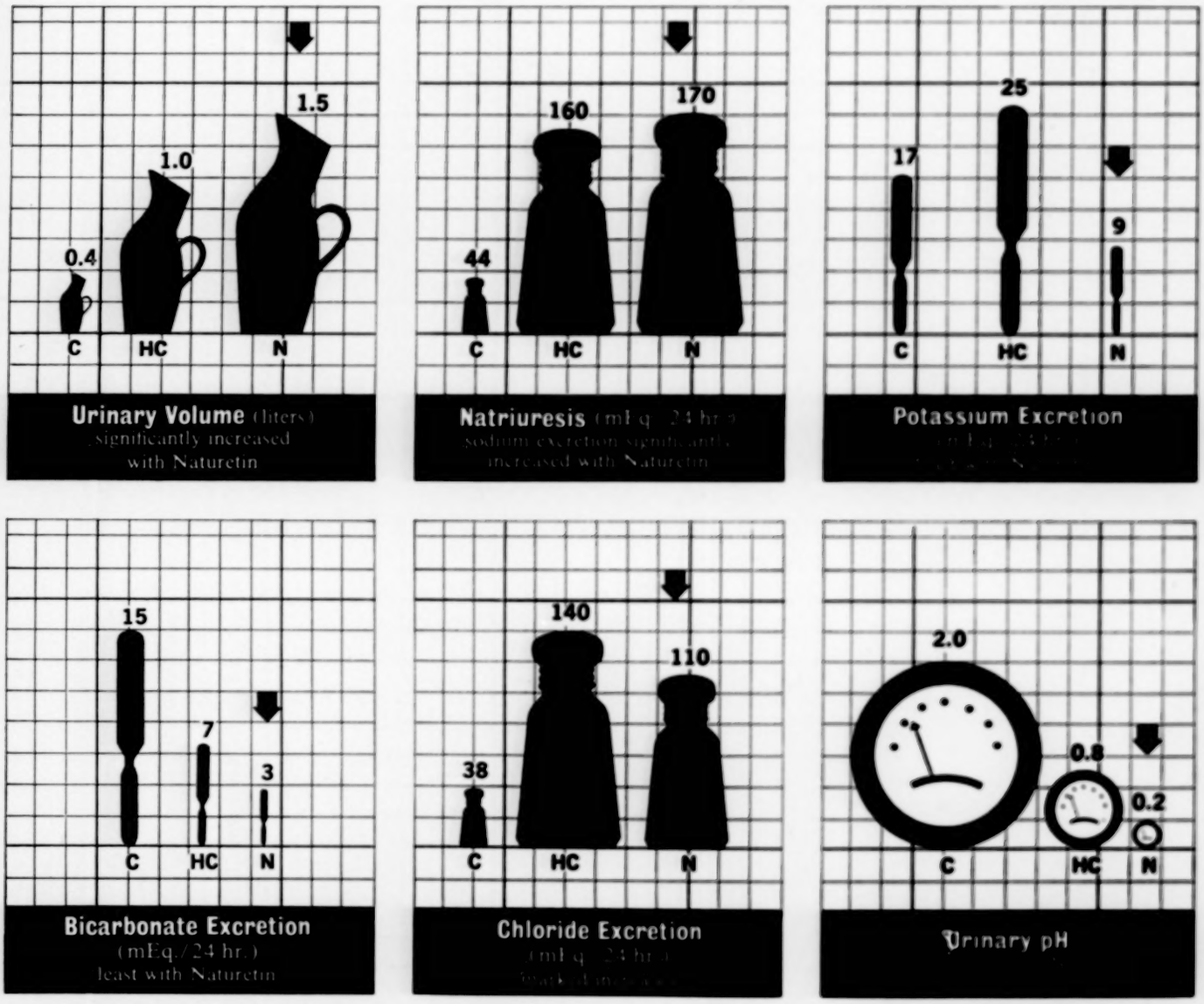
more closely approaches the ideal diuretic

Naturētin

Squibb Benzydroflumethiazide

"When compared to other members of this heterocyclic group of compounds, this drug [NATURETIN] shows a significantly increased natriuresis and decreased loss of potassium and bicarbonate. In this respect it more closely approaches a natural or 'ideal diuretic.' It is effective upon continuous administration and causes no significant serum biochemical changes. It is effective in a wide variety of edematous and hypertensive states and represents a significant advance in diuretic therapy." *Ford, R.V.: Pharmacological observations on a more potent benzothiadiazine diuretic; accepted for publication by the American Heart Journal.*

Comparison of electrolyte excretion pattern for the 24 hours following typical doses of chlorothiazide, hydrochlorothiazide, and Naturetin[1]



Typical Doses: Chlorothiazide—1,000 mg.; Hydrochlorothiazide—50 mg.; Naturetin (Benzydroflumethiazide)—5 mg.

1. *Adapted from: Ford, R. V., Squibb Clin. Rev. Notes 2:1 (Dec.) 1959.*

A single 5 mg. tablet once a day provides all these advantages[2]

- prolonged action – in excess of 18 hours
- convenient once-a-day dosage
- low daily dosage – more economical for the patient
- no significant alteration in normal electrolyte excretion pattern
- repetitively effective as a diuretic and antihypertensive
- greater potency mg. for mg.—more than 100 times as potent as chlorothiazide
- potency maintained with continued administration
- low toxicity – few side effects – low salt diets not necessary
- comparative studies with chlorothiazide, hydrochlorothiazide, and Naturetin disclose that smallest doses of Naturetin produce greater weight loss per day
- in hypertension, Naturetin, alone or in combination with other anti-hypertensives, produces significant decreases in mean blood pressure and other favorable clinical effects
- purpura and agranulocytosis not observed
- allergic reactions rarely observed

[2]Reports (1959) to the Squibb Institute for Medical Research.

Naturetin – *Indications:* in control of edema when diuresis is required, in congestive heart failure, in the premenstrual syndrome, nephrosis and nephritis, cirrhosis with ascites, edema induced by drugs (certain steroids); in the management of hypertension, used alone, combined with Raudixin (Squibb Rauwolfia Serpentina Whole Root), or with other antihypertensive drugs, such as ganglionic blocking agents.

Contraindications: none, except in complete renal shutdown.

Precautions: when Naturetin is added to an antihypertensive regimen including hydralazine, veratrum, and/or ganglionic blocking agents, immediate reduction must be made in the dosage for all preparations; the dosage for ganglionic blocking agents must be decreased by 50% to avoid a precipitous drop in blood pressure. This also applies if these hypotensive drugs are added to an established Naturetin regimen . . . in hypochloremic alkalosis with or without hypokalemia . . . in cirrhotic patients or those on digitalis therapy when reductions in serum potassium are noted . . . in diabetic patients or those predisposed to diabetes . . . when increased uric acid concentrations are noted . . . when signs – leg or abdominal cramps, pruritus, paresthesia, rash – suggestive of hypersensitivity, are noted.

Naturetin – *Dosage: in edema,* average dose, 5 mg., once daily, preferably in the morning; to initiate therapy, up to 20 mg., once daily or in divided doses; for maintenance, 2.5 to 5.0 mg., daily in a single dose. *In hypertension:* suggested initial dose, 5 to 20 mg. daily; for maintenance, 2.5 to 15 mg. daily, depending on the individual response of the patient. When Naturetin is added to an antihypertensive regimen with other agents, lower maintenance doses of each drug should be used.

Naturetin – *Supplied:* tablets of 2.5 mg. and 5 mg. (scored).

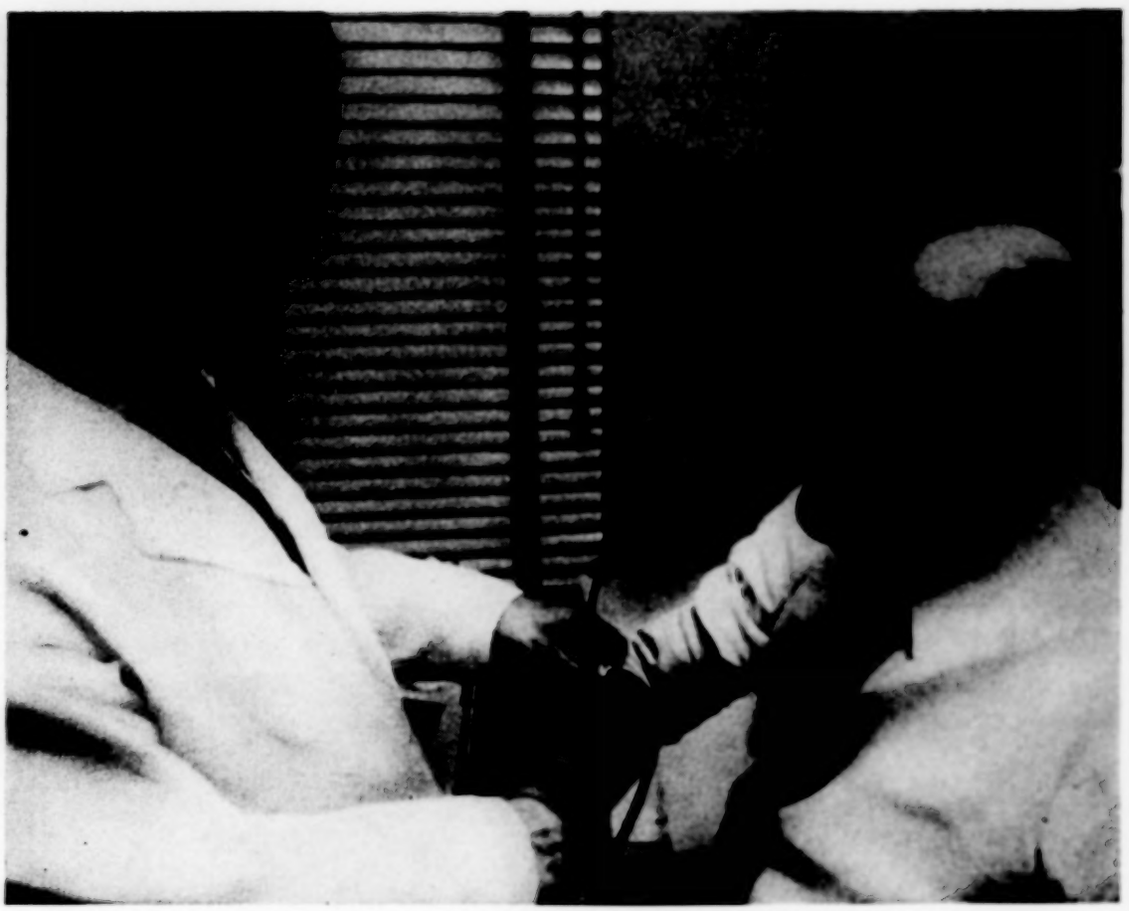
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Squibb Quality—the Priceless Ingredient

Rx Naturetin 5mg. Disp. #30 Sig: 1 each morning

"RAUDIXIN"® AND "NATURETIN" ARE SQUIBB TRADEMARKS.

Why so many hypertensive patients prefer **Singoserp**:



2/2782MK

CIBA

It spares them the usual rauwolfia side effects

FOR EXAMPLE: "A clinical study made of syrosingopine [Singoserp] therapy in 77 ambulant patients with essential hypertension demonstrated this agent to be effective in reducing hypertension, although the daily dosage required is higher than that of reserpine. Severe side-effects are infrequent, and this attribute of syrosingopine is its chief advantage over other Rauwolfia preparations. The drug appears useful in the management of patients with essential hypertension."[1]

Almost all side effects relieved when Singoserp was substituted for other rauwolfia derivatives in 24 patients[2]

Side Effects	Incidence with Prior Rauwolfia Agent	Relieved by Singoserp	Not Relieved*
Depression	11	10	1
Lethargy or fatigue	5	5	0
Nasal congestion	7	7	0
Gastrointestinal disturbances	2	0	2
Conjunctivitis	1	1	0

*Two of the 24 patients had two troublesome side effects.

Singoserp®

(syrosingopine CIBA)

First drug to try in new hypertensive patients

First drug to add in hypertensive patients already on medication

Supplied: **Singoserp *Tablets*, 1 mg. (white, scored); bottles of 100.**

1. Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. *169*:1609 (April 4) 1959.
2. Bartels, C. C.: N. E. J. Med. *261*:785 (Oct. 15) 1959.

Lifts depression....



An emotionally balanced patient
Thanks to your treatment and the help of Deprol, her depression is relieved and her anxiety and tension calmed. She eats well, sleeps well, and can return to her normal activities.

as it calms anxiety!

Deprol helps balance the mood by lifting depression as it calms related anxiety

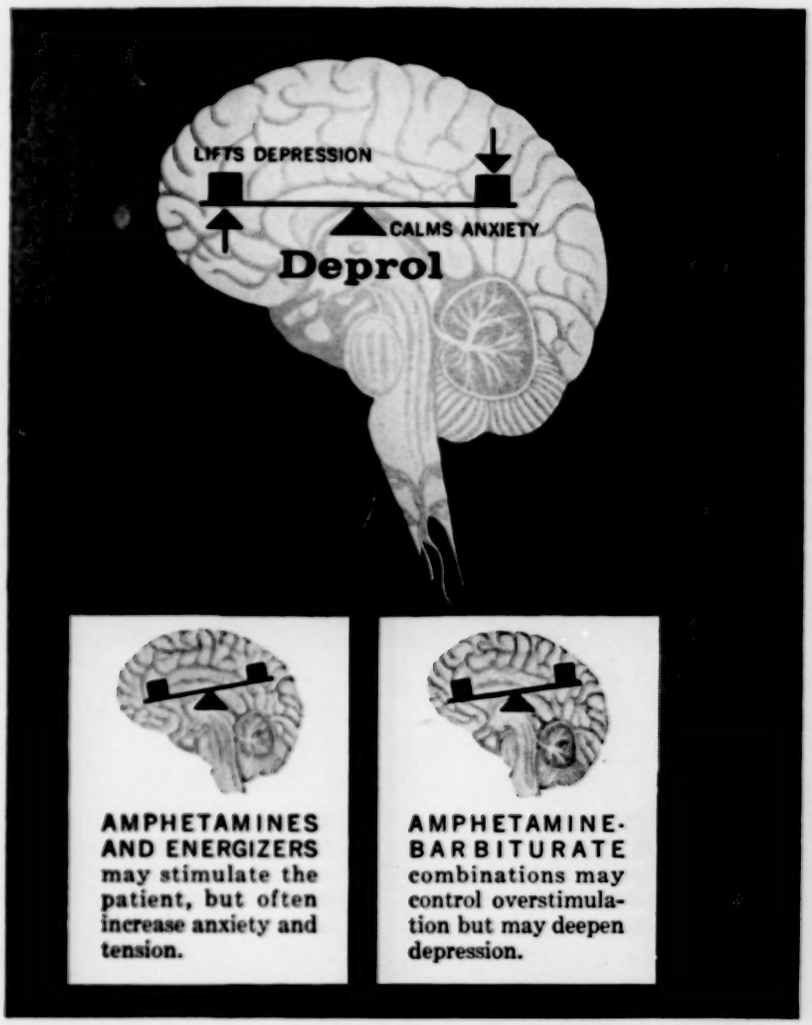
No "seesaw" effect of amphetamine-barbiturates and energizers

While amphetamines and energizers may stimulate the patient—*they often aggrarate anxiety and tension.* And although amphetamine-barbiturate combinations may counteract excessive stimulation—*they often deepen depression.*

In contrast to such "seesaw" effects, Deprol lifts depression as it calms anxiety—both at the same time.

Safer choice of medication than untested drugs

Deprol does not produce hypotension, liver damage, psychotic reactions or changes in sexual function.



BIBLIOGRAPHY: 1. Alexander, L.: Chemotherapy of depression—Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. *J.A.M.A.* 166:1019, March 1, 1958. 2. Balsman, J. C. and Carlton, H. N.: Deprol as adjunctive therapy for patients with advanced cancer. Antibiotic Med. & Clin. Therapy. In press, 1959. 3. Bell, J. L., Tauber, H., Santy, A. and Fulito, F.: Treatment of depressive states in office practice. Dis. Nerv. System 20:263, June 1959. 4. McClure, C. W., Pazos, P. N., Soeare, G. S., Fulman, E., Slatters, J. J., Korefal, S. H., Hansen, B. S., Wand, C. A. and Corenia, G. S.: Treatment of depression—New technics and therapy. Am. Pract. & Digest Treat. In press, 1959. 5. Pennington, V. M.: Meprobamate-benactyzine (Deprol) in the treatment of chronic brain syndrome, schizophrenia and senility. J. Am. Geriatrics Soc. 7:656, Aug. 1959. 6. Ricketts, H. and Ewing, J. H.: Deprol in depressive conditions. Dis. Nerv. System 20:364, (Section One), Aug. 1959. 7. Rothenberger, A.: Use of Deprol (meprobamate combined with benactyzine hydrochloride) in the office treatment of depression. M. Ann. District of Columbia 28:438, Aug. 1959. 8. Settel, E.: Treatment of depression in the elderly with a meprobamate-benactyzine hydrochloride combination. Antibiotic Med. & Clin. Therapy. In press, 1959.

^Deprol^

DOSAGE: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.

COMPOSITION: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.

SUPPLIED: Bottles of 50 light-pink, scored tablets. Write for literature and samples.

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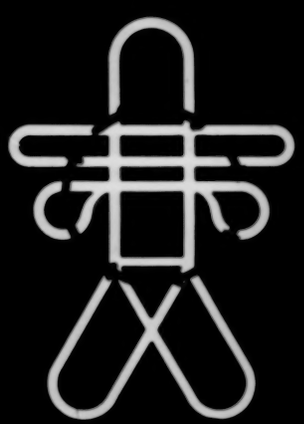
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DISSOLVES INTRAVASCULAR

NOT JUST A NEW DRUG... *A NEW THERAPY*

TRADEMARK

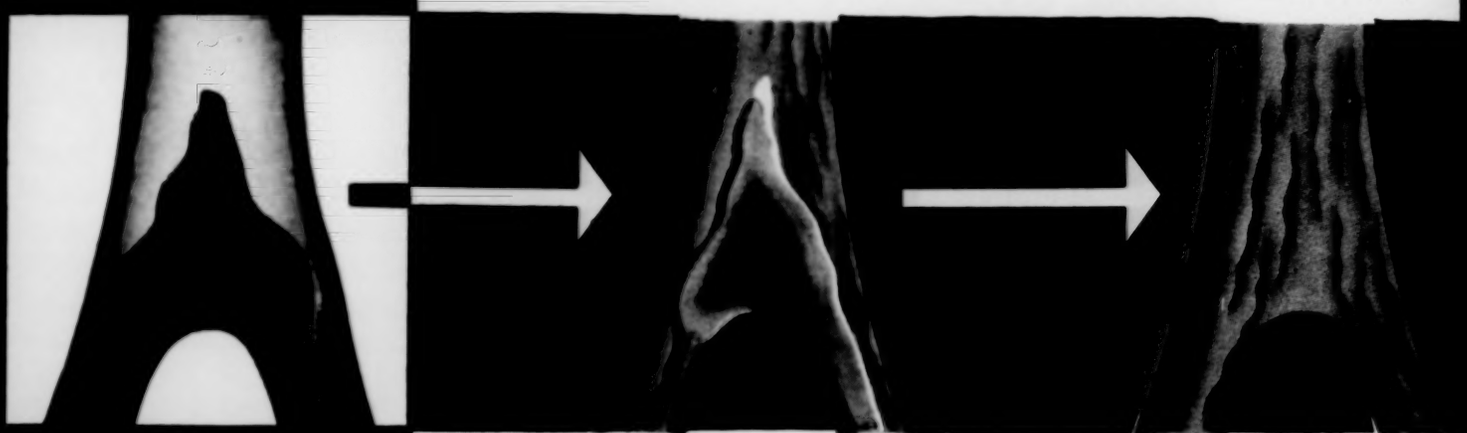
Fibrinolysin (Human)



ORTHO PHARMA[illegible]

CLOTS

in thrombophlebitis and pulmonary embolism



Clinically proved,[1-3] ACTASE has a specific lytic effect upon the venous thrombus or pulmonary embolus. Patients respond rapidly, often dramatically, to the clot-dissolving action of an intravenous infusion of this physiologic fibrinolysin.[4] A significant decrease in length of hospitalization following thrombophlebitis, as well as a reduction in the threat of pulmonary embolism, is now possible. In one series of patients with deep thrombophlebitis, some of whom had previously suffered pulmonary emboli, no occurrence of pulmonary emboli was reported following administration of ACTASE[1]

COMPLETE INFORMATION AVAILABLE ON REQUEST.

Ortho



Mrs. C.R. is Normotensive with Singoserp/Esidrix...

Relieved of hypertensive headache, patient can now carry out heavy responsibilities

Severe headache—a symptom of her hypertension—has troubled Mrs. C. R. for about 4 years. Her job and home life have imposed additional stress. Employed by a chocolate manufacturer—on the "swing shift"—she works in a cold room, wearing a coat and wool socks as protection. After work she waits a half hour for a bus that gets her home at 1:30 a.m.

Mornings at home offer no respite. Since her husband, a cardiac cripple, cannot help with household chores, she does the cleaning and shopping, also works on the lawn and garden. Mrs. R. and her husband built their own house from the foundation up some years ago. After his incapacitating heart attack in 1957 she poured the concrete walks and patio herself.

Initially, Mrs. R.'s physician prescribed meprobamate and chlorothiazide, with no effect. On January 29, 1959, she was switched to Esidrix 50 mg. in combination with Singoserp 0.5 mg. daily;

Before treatment: B. P. 190/110 mm. Hg



After treatment: B. P. 140/80 mm. Hg



her blood pressure was then 190/110 mm. Hg.

By March 9, Singoserp/Esidrix combination therapy had lowered Mrs. R.'s pressure to 150/100 mm. Hg. On June 1, the reading was 140/80 mm. Hg. As of August 24, the patient's blood pressure had stabilized at that normotensive level.

Mrs. R. is delighted with the results of Singoserp/Esidrix treatment. Her headaches are gone. She once again has the energy to handle her heavy responsibilities at work and at home.

With Singoserp-Esidrix you give your hypertensive patients the benefits of potentiated therapy. Often more effective than a single drug, Singoserp-Esidrix usually relieves hypertension without side effects. Indicated in mild to moderate hypertension.

SUPPLIED: Singoserp-Esidrix *Tablets #2* (white), each containing 1 mg. Singoserp and 25 mg. Esidrix. *Tablets #1* (white), each containing 0.5 mg. Singoserp and 25 mg. Esidrix.

Singoserp®-Esidrix®

(syrosingopine and hydrochlorothiazide CIBA)

Combination Tablets

POTENTIATED ANTIHYPERTENSIVE



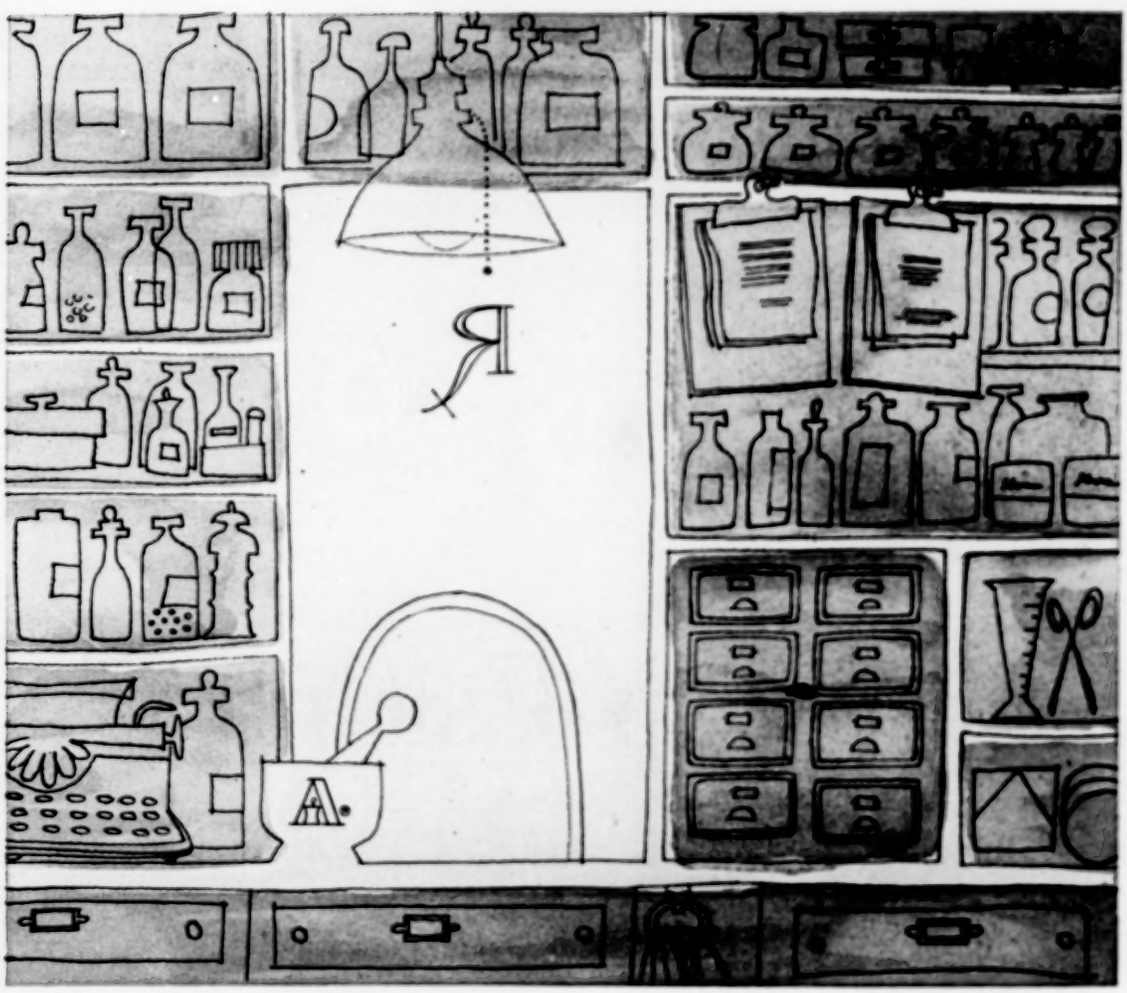
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NO OTHER THYROID PRODUCT

is used so widely and so often . . . stocked by so many leading pharmacies . . . regarded throughout the world as the pioneer in thyroid standardization and the original standard of comparison for all thyroid preparations

ALWAYS SPECIFY ARMOUR THYROID



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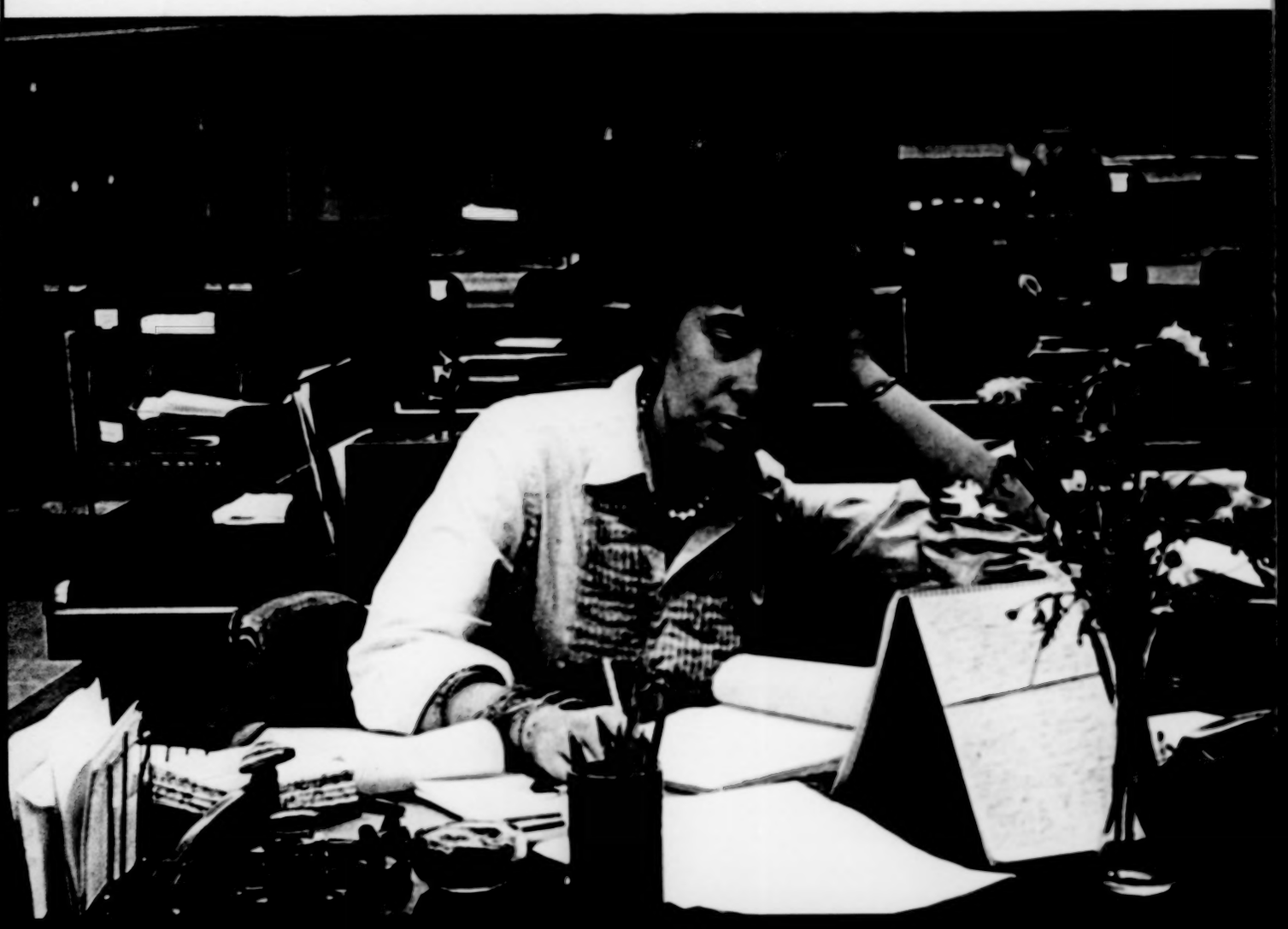
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Ford, Ralph V.: Southern Med. Jl. 52: 40, (Jan.) 1959

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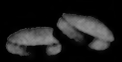
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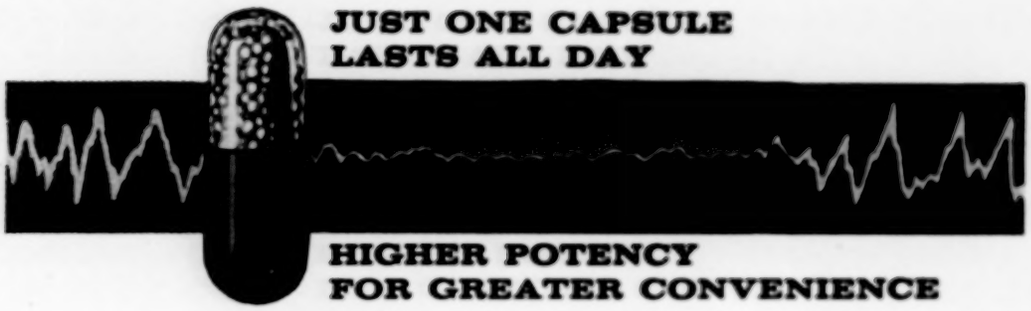
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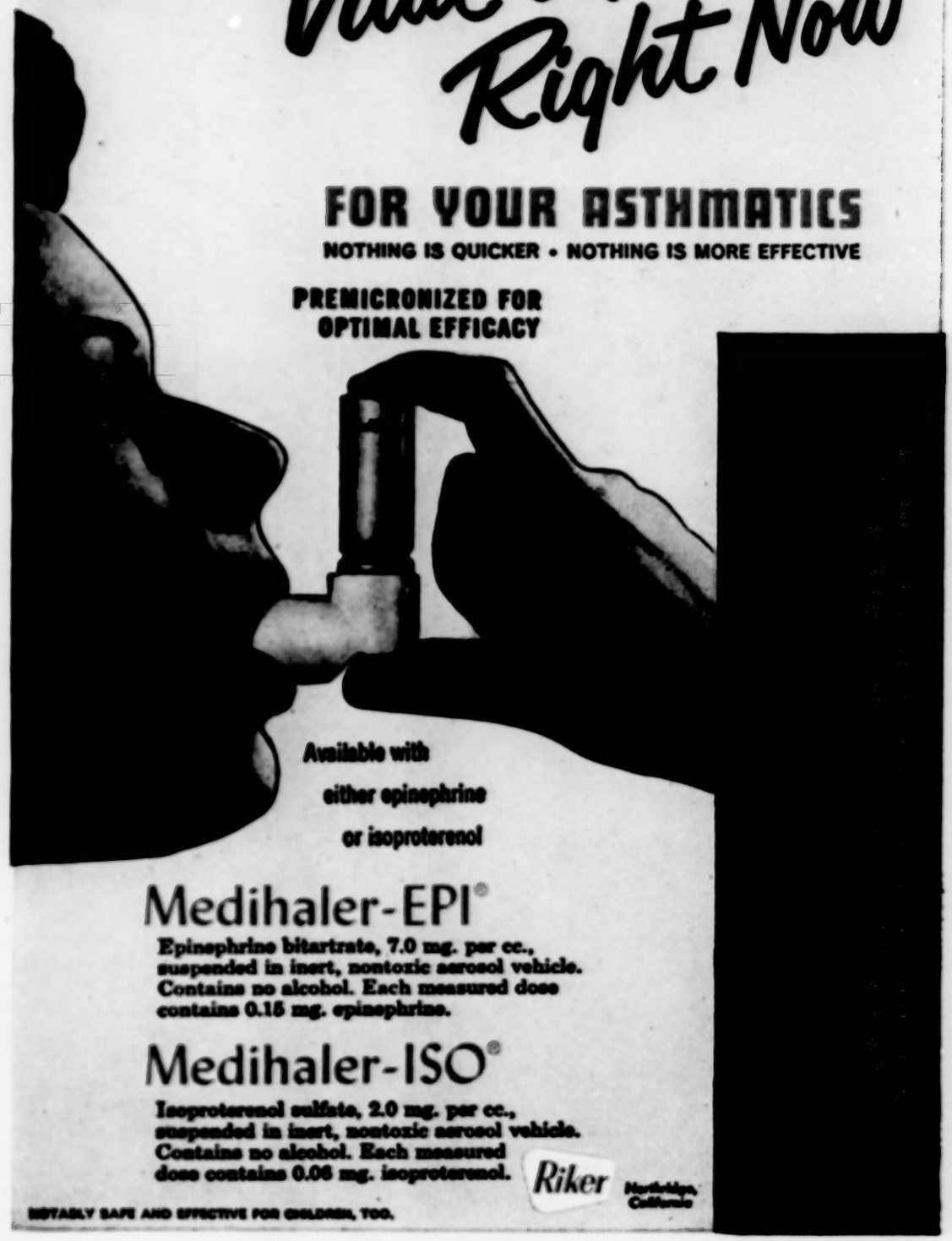
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*Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. 169:1609 (April 4) 1959.

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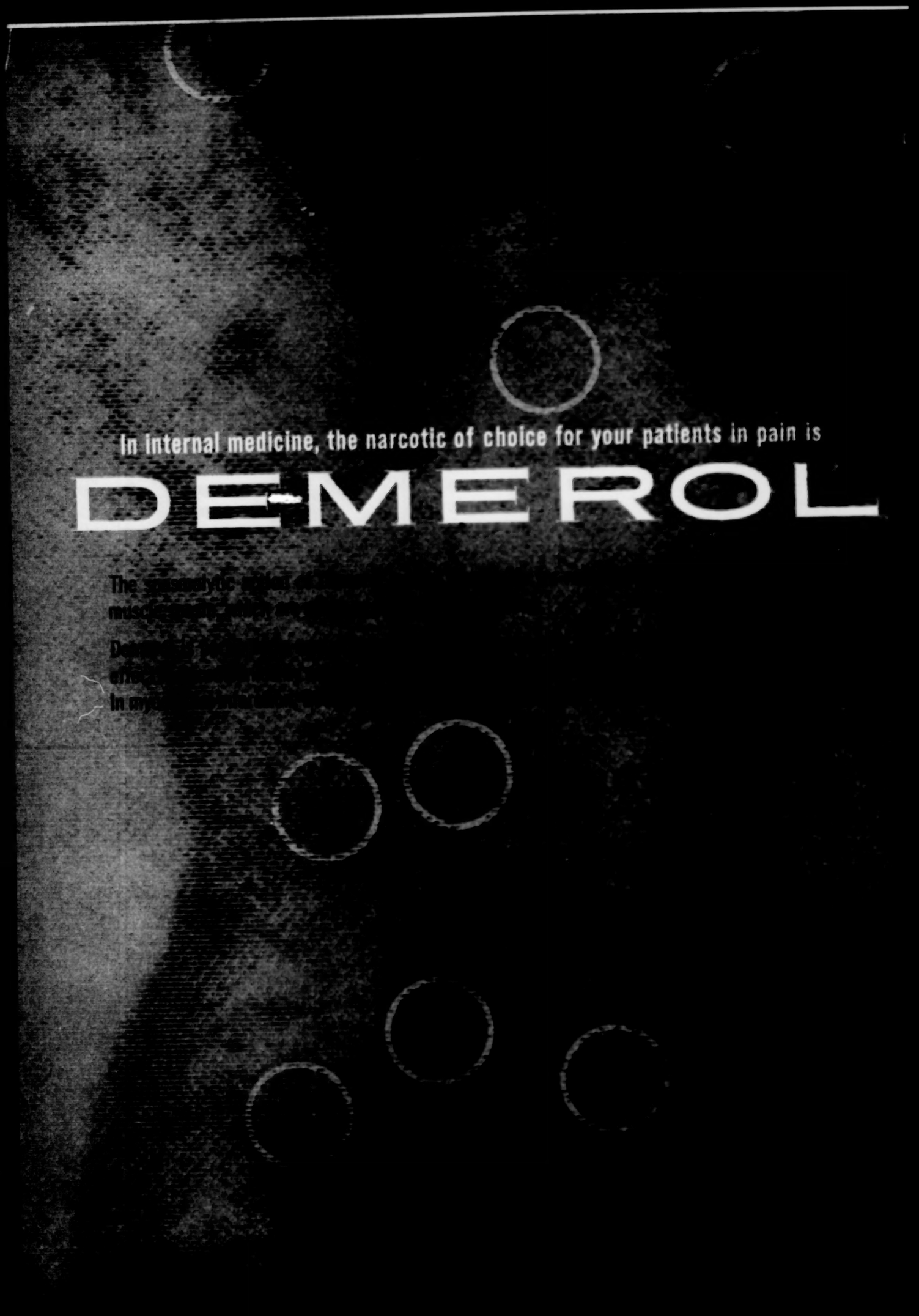
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Renal Acidosis . . . . . J. RUSSELL ELKINTON 165

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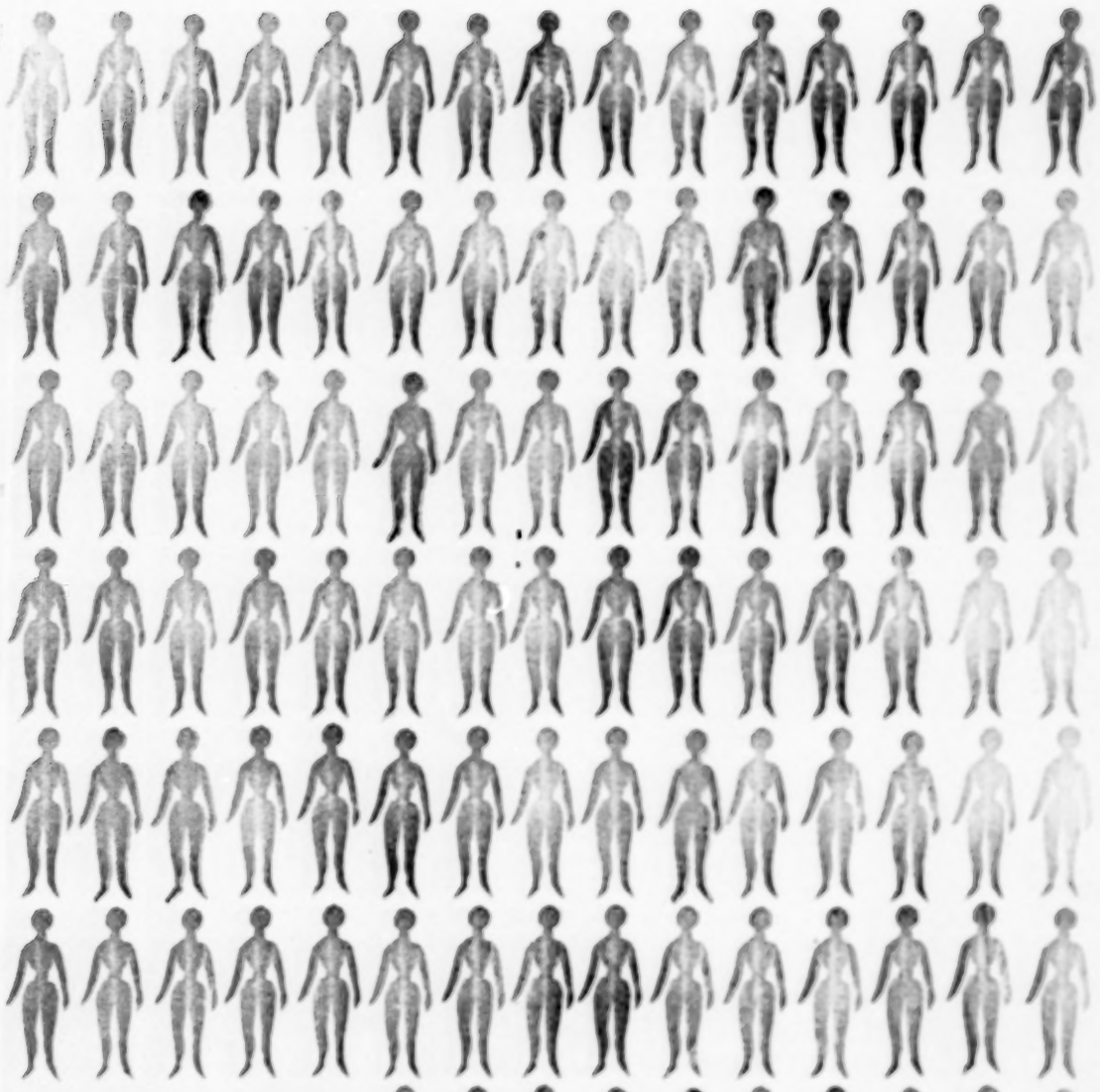
The Diagnosis and Treatment of Renal Hypertension. With Special Reference to a Case of Hypertension Due to Stenosis of Both Renal Arteries
E. R. YENDT, W. K. KERR, D. R. WILSON AND Z. F. JAWORSKI 169

There has been a lively resurgence of interest in surgical correction of renal hypertension resulting from anomalies reproducing the Goldblatt phenomenon, and the present study validates this interest. The authors recount their experience with twenty patients subjected either to nephrectomy or, when feasible, to renal artery repair for relief of renal hypertension. The diagnosis, which requires a high index of suspicion, was based for the most part on differential studies of urinary volume and sodium excretion by the two kidneys and/or on aortography; the usual methods of examination of renal function do not suffice. Three of the patients, one described in detail, had bilateral renal artery stenosis. It is considered that surgical intervention was successful in twelve of the twenty patients, all presumed to be retractory to medical therapy. However, success in diagnosis and management, as is made abundantly clear, requires meticulous attention to detail in both medical and surgical aspects of patient care.

Effect of Thoracolumbar Sympathectomy on the Clinical Course of Primary (Essential) Hypertension. A Ten-year Study of 100 Sympathectomized Patients Compared with Individually Matched, Symptomatically Treated Control Subjects
KENNETH A. EVELYN, MADAN M. SINGH, WILLIAM P. CHAPMAN, GEORGE A. PERERA AND H. THALER 188

This collaborative, large scale, long term study of the effects of thoracolumbar sympathectomy on the course of essential hypertension omits no device, in experimental design or in statistical analysis, to achieve an impartial and objective evaluation. The results of a ten-year follow-up of 100 surgically treated patients are compared with those of 100 matched control subjects treated symptomatically, i.e., without antihypertensive drugs. The findings are thus of interest in respect to the natural history of essential hypertension, which is described in some detail as well as in connection with the results of sympathectomy. The data are in general agreement with previous reports but are more complete and, in some respects, disillusioning. Surgery convincingly reduced hypertension (average decrease, 21 mm. Hg systolic, 15 mm. Hg diastolic) and with this, papilledema and retinopathy, probably also had some preventative effect on renal deterioration. There was no significant difference between the surgically and medically treated patients, however, in the incidence of cardiac failure, myocardial infarction, cerebrovascular accidents, mean survival

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*Murphy, H. S., *et al.*, Scientific Exhibit, A.M.A. Dec. 1-4, 1958, Dallas, Texas.

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time or mortality rate (41 per cent of the surgical series dead at the end of ten years, 47 per cent of the control subjects). Thoracolumbar sympathectomy has an unquestioned place in the management of essential hypertension but, balancing up postoperative gains against disabilities, the authors conclude that "the over-all effect of the operation on morbidity and mortality in this small consecutive series of cases was somewhat disappointing."

Testicular Lesions of Periarteritis Nodosa, with Special Reference to Diagnosis
ELMER V. DAHL, ARCHIE H. BAGGENSTOSS AND JAMES H. DEWEERD 222

In view of the uncertainties of muscle biopsy as a means of diagnosis in periarteritis nodosa, the suggestion of testicular biopsy in appropriate cases is of interest. The suggestion is based on the substantial incidence of testicular lesions found at autopsy, and the authors predict that some 20 per cent of testicular biopsies in patients with periarteritis nodosa should yield diagnostic results. This is not recommended as a routine procedure but when testicular symptoms are or have been present.

Aldosterone Excretion in Hypopituitarism and After Hypophysectomy in Man
E. J. ROSS, W. VAN'T HOFF, J. CRABBÉ AND G. W. THORN 229

There has been some difference of opinion as to the complete corticotropin-independence of aldosterone excretion, and of the effects of hypophysectomy. These differences are resolved, in part, by the present study. Patients with panhypopituitarism of long standing excrete significantly less than normal quantities of aldosterone in the urine but for some time after hypophysectomy may show enhanced aldosterone excretion, in association with the large volumes of urine passed (diabetes insipidus). It is assumed that the adrenotropic effect of corticotropin maintains the capacity of the adrenal cortex to form and release aldosterone in greater or lesser measure.

Hyperventilation and Arterial Hypoxemia in Cirrhosis of the Liver
H. O. HEINEMANN, C. EMIRGIL AND J. P. MIJNSSEN 239

Arterial hypoxemia and hyperventilation were shown by the authors to be present simultaneously in patients with cirrhosis of the liver. Careful pulmonary function studies excluded diffusing difficulty as an explanation for the hypoxemia. An increase in venous admixture, best explained by assuming portal to pulmonary vein anastomoses, is advanced as the mechanism for the hypoxemia. Careful analysis of the factors affecting pulmonary ventilation failed to reveal any satisfactory explanation for the hyperventilation observed.

Coincidence of Patent Ductus Arteriosus and Rheumatic Heart Disease, with a Comment on the "Postcommissurotomy Syndrome"
JOHN A. BOONE AND ROBERT M. ROSEMOND 247

The development of what appears to be overt rheumatic heart disease in an appreciable proportion of patients operated on for patent ductus arteriosus suggests a predilection for rheumatic fever under these circumstances, as would seem to be true of many congenital heart anomalies. The point stressed is that postoperative observation should be particularly alert to the possibility of rheumatic heart disease, and that perhaps regular antibiotic prophylaxis should be instituted.

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new for total management of itching,[1,2] inflamed,[3,4] infected[5,6] skin lesions



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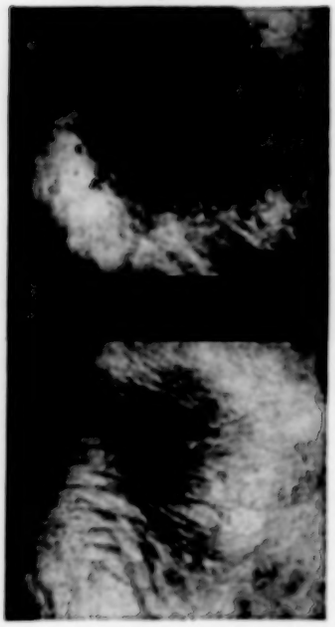
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References: 1. Sheimire, J.B., Jr.: Monographs on Therapy 3:164 (Nov.) 1958. • 2. Nix, T.E., Jr., and Derbes, V.J.: Monographs on Therapy 3:123 (Nov.) 1958. • 3. Robinson, R.C.V.: Bull. School of Med., U. Maryland 43:54 (July) 1958. • 4. Sternberg, T.H.; Newcomer, V.D., and Reisner, R.M.: Monographs on Therapy 3:115 (Nov.) 1958. • 5. Clark, P.F., and Hallett, J.J.: Monographs on Therapy, 3:153 (Nov.) 1958. • 6. Smith J.G., Jr.; Zawisza, R.J., and Blank, H.: Monographs on Therapy, 3:111 (Nov.) 1958. • 7. Monographs on Therapy, 3:137 (Nov.) 1958. • 8. Howell, C.M., Jr.: North Carolina M.J. 19:449 (Oct.) 1958. • 9. Bereston, E.S.: South. M.J. 50:547 (April) 1957.

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Chronic Active Pulmonary Histoplasmosis with Cavitation. A Clinical and Laboratory Study of Thirteen Cases

DAVID F. LOEWEN, JOHN J. PROCKNOW AND CLAYTON G. LOOSLI 252

While it is generally appreciated that pulmonary histoplasmosis may follow a prolonged active course, with cavitation, and closely simulate tuberculosis, detailed documentation has been sparse. This is amply provided in the present study, which summarizes the case histories of thirteen such patients. It is readily understandable from the history, physical findings and roentgenograms of these cases that they are commonly confused with tuberculosis. The differential diagnosis can be established only by demonstration of histoplasmic infection by means of skin tests, serological reactions or (conclusively) by culture of the fungus. Failure to demonstrate acid-fast bacilli should lead to suspicion of fungal infection, but since many patients are consigned to tuberculosis sanatoriums in error, they are likely to contract tuberculosis there if not already infected.

The Postpneumonectomy State. Clinical and Physiologic Observations in Thirty-Six Cases

BENJAMIN BURROWS, ROBERT W. HARRISON, WILLIAM E. ADAMS, ELEANOR M. HUMPHREYS, EDWIN T. LONG AND ARTHUR F. REIMANN 281

Extensive pulmonary resection has become an important therapeutic measure in recent years, and the adequacy of pulmonary function after pneumonectomy is therefore a question of some practical significance. The present study is one of relatively few performed in adults sufficiently long after ablation of the lung. Pulmonary overinflation in the remaining lung was commonly observed but did not, in the majority of patients, result in significant exercise intolerance, or in destructive changes in the remaining lung. When respiratory difficulty was encountered, it was attributed to a complicating cardiac or pulmonary disorder. Of considerable physiologic interest was a demonstrable reduction in diffusing capacity. As a result of pneumonectomy, the cardiac output passed through the remaining lung but this did not result in significant pulmonary hypertension unless the remaining lung was abnormal.

Clinicopathologic Conference

Severe Abdominal Pain with Negative Physical and Laboratory Findings . . . 298

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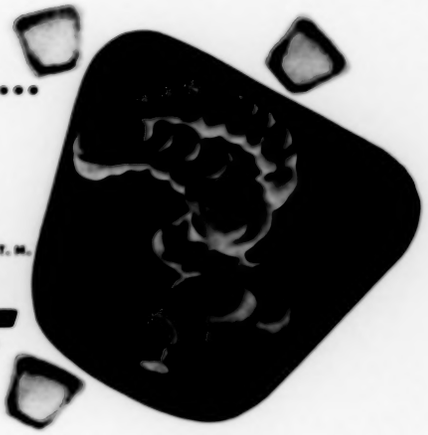
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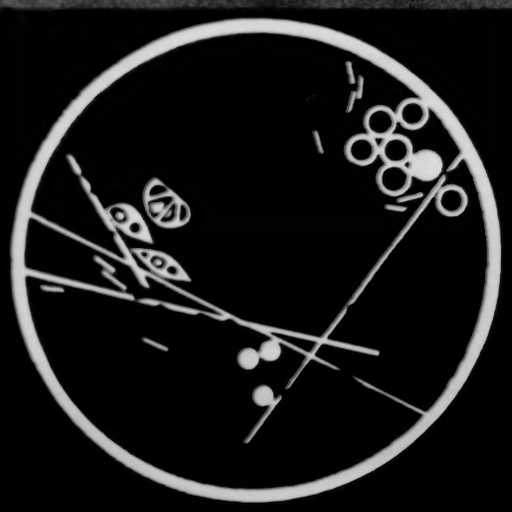
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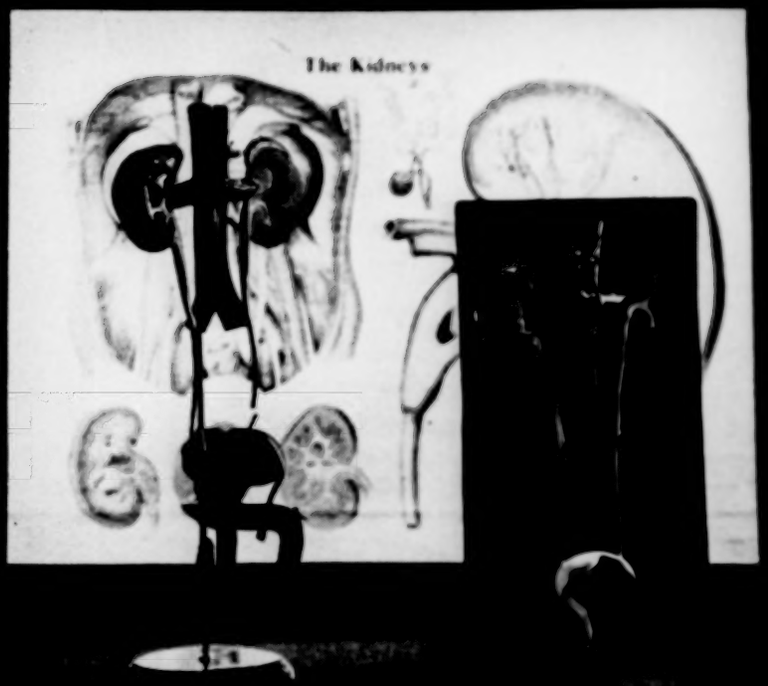
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"In order of decreasing effectiveness, the activity of the drugs against gram-negative organisms was as follows: nitrofurantoin, chloramphenicol, tetracycline, streptomycin, and sulfisoxazole."

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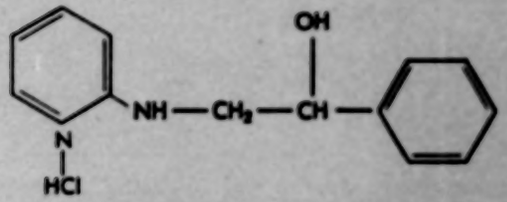
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Batterman, Grossman and Mouratoff[4] compared Analexin with aspirin, sodium salicylate and a placebo in a series of 195 patients with various painful conditions. The authors concluded:

"Not only is satisfactory relief of painful states achieved in the majority of patients regardless of etiology and duration of pain, but there is also no evidence suggestive of cumulative toxicity. Furthermore, in contrast to codeine and meperidine, the likelihood of untoward reactions occurring in ambulant patients is not high. This is a decided advantage since the control of pain in the ambulant patient with chronic pain is a major clinical problem."

"Phenyramidol (Analexin), with therapeutic doses is not only safe for chronic administration, but also to date we have noted no adverse effect upon the cardiovascular, gastrointestinal, respiratory, kidney, liver or central nervous systems."

Wainer[5] reported a series of 200 cases treated with phenyramidol for various painful conditions. In fifty of these patients who had dysmenorrhea, he saw excellent results in 40, good results in 5 and poor results in 5. Further examination in 4 cases not responding revealed presence of organic pathology. A second group of 50 cases with headache and associated premenstrual tension responded with over-all excellent results. Wainer also reports the use of phenyramidol to replace codeine for postpartum pain and describes 100 cases wherein a combination of phenyramidol with aluminum aspirin (Analexin-AF) successfully replaced aspirin and codeine therapy.

more results with analexin in clinical trials

In another series of dysmenorrhea cases, Bader[7] compiled data on 20 employees of a telephone company who required ½ to 2 days off from work every month regardless of prior therapy employed. Satisfactory results were achieved in 15 out of 20 and a fair response in the remaining five. All were able to remain on the job although relief was not complete in the latter cases.

Bealer[8] treated 32 patients with phenyramidol mostly for musculoskeletal disorders and had good or very good results in 15, fair results in 14 and poor or inconclusive results in 2 patients. Cohen[9] used phenyramidol together with aspirin in 15 patients with such conditions as sciatic pain, osteoarthritis, anterior chest wall syndrome, etc. and got outstanding relief in 80 per cent. Gilbert[10] reported that 15 patients with nonspecific headache had excellent relief in a matter of minutes with phenyramidol, and in 8 cases of dry socket pain Bruno[11] reports immediate relief in six cases and good results later in the other two after sockets were curetted under local anesthesia. Stern[12] reported on 40 ambulatory cases with a variety of painful conditions and saw good relief in 32 patients and poor in 8. Results were best in acute sacroiliac pain, myositis, muscle spasm, fractures, pleurisy and neuritis. Ten of 13 patients with osteoarthritis responded very well and are continuing on phenyramidol therapy.

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analexin *(phenyramidol)*
for relief of pain *and muscle tension* in:
low back pain
sprains and strains
myalgia
glass arm
wry neck
osteoarthritis
dysmenorrhea
tension headache
gout
postpartum pain
epigastric distress
(pylorospasms, gastritis, duodenal ulcer, cholecystitis)
genitourinary conditions
(premenstrual cramping or tension)
abdominal distress
(flatulence, colic)
toothache and dry socket pain

analexin-AF *(phenyramidol with aluminum aspirin)*
for relief of pain and muscle tension also involving inflammatory processes and/or fever, as in:
arthritis
arthralgia
bursitis
tendinitis
myalgia of strain and tear
pre- and postoperative toothache

dosage:
analexin: for relieving pain and/or muscle tension, one or two tablets every 4 hours. In dysmenorrhea, two tablets initially then one tablet every 2 to 4 hours as needed.

analexin-AF: two tablets every 4 hours or as required.

supply:
analexin tablets—Each tablet contains 200 mg. of phenyramidol HCl. Bottles of 100 tablets.

analexin-AF tablets — Each tablet contains 100 mg. of phenyramidol HCl and 300 mg. of aluminum aspirin. Bottles of 100 tablets.

REFERENCES: 1. O'Dell, T. B.; Wilson, L. B.; Napoli, M. D.; White, H. D., and Minsky, J. H.: J. Pharmacol. & Exper. Therap., in press. 2. O'Dell, T. B.; Wilson, L. B.; Napoli, M. D.; White, H. D., and Minsky, J. H.: Fed. Proc. 18:1694, 1959. 3. Gray, A. P. and Heitmeier, D. E.: J. Am. Chem. Soc. 81:4347, 1959. 4. Gray, A. P. and Heitmeier, D. E.: J. Am. Chem. Soc. 81:4351, 1959. 5. Batterman, R. C.; Grossman, A. J., and Mavretalli, G. J.: Am. J. Med. Sc. 238:315, 1959. 6. Weiner, A. E.: The Use of Phenyramidol in Obstetrics and Gynecology. Read before the New York Academy of Sciences, Dec. 8, 1959. 7. Bader, G.: Clinical Report 511; 598. 8. Bosler, J. D.: Clinical Report 511; 592. 9. Cohen, B. M.: Clinical Report 511; 596. 10. Gilbert, E.: Clinical Report 511; 597. 11. Bruns, E. A.: Clinical Report 511; 593. 12. Stern, E.: Clinical Report 511; 599.
Clinical Reports cited above are in the files of the Medical Department, Irwin, Neisler & Co.

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*Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. 169:1609 (April 4) 1959.

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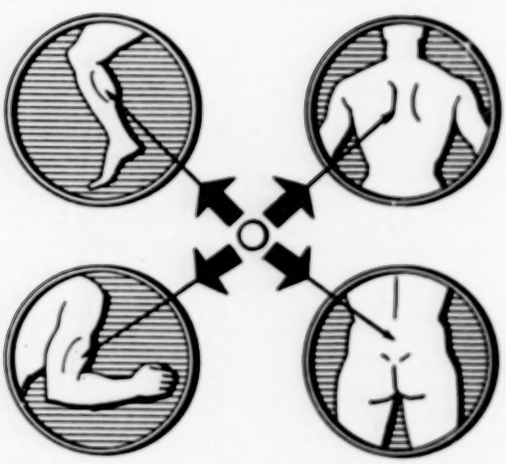


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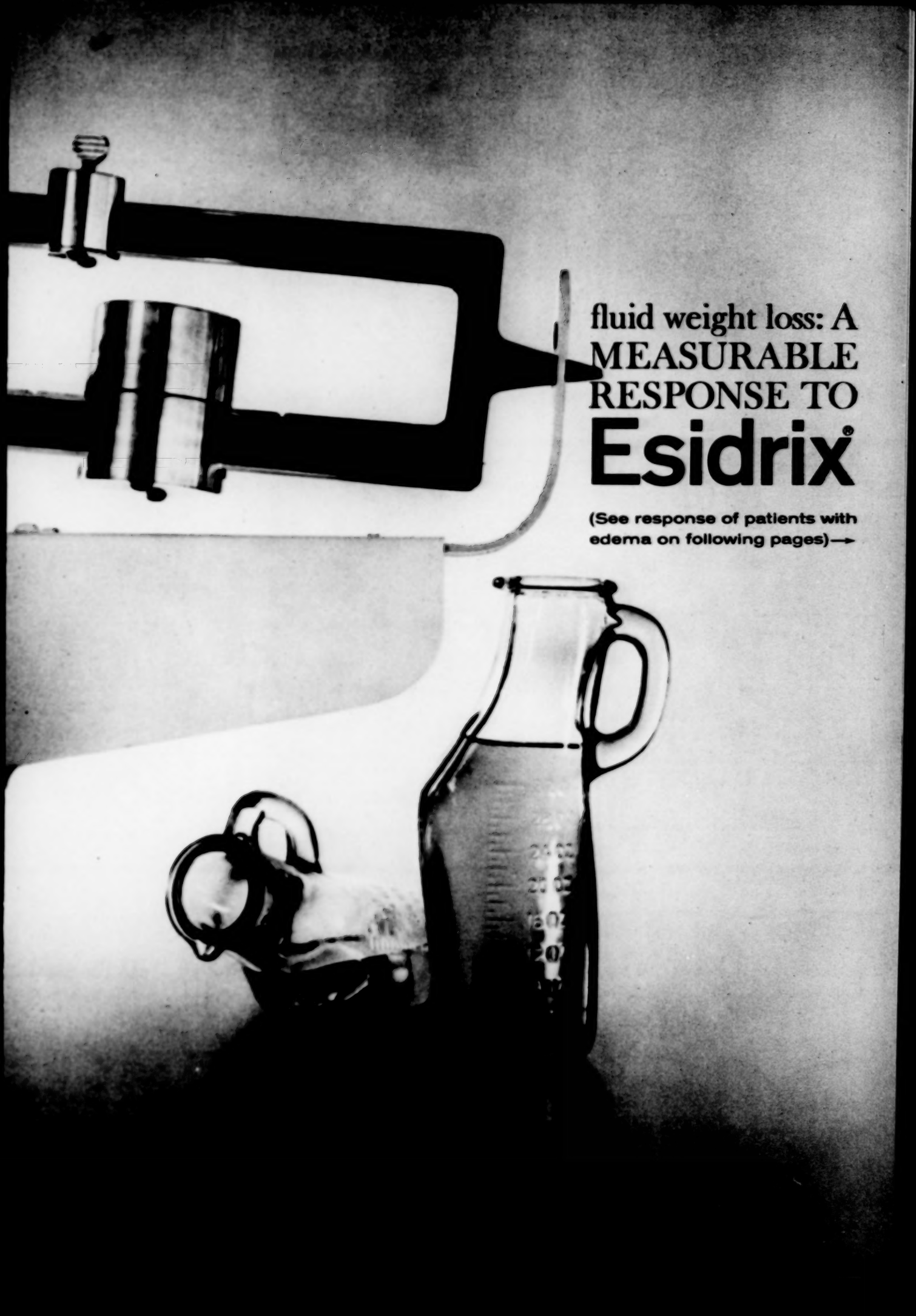
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asthma and
4+ pitting
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5 pounds lost in 4 days; 4+ pitting cleared; hepatic congestion and râles cleared; patient ambulatory





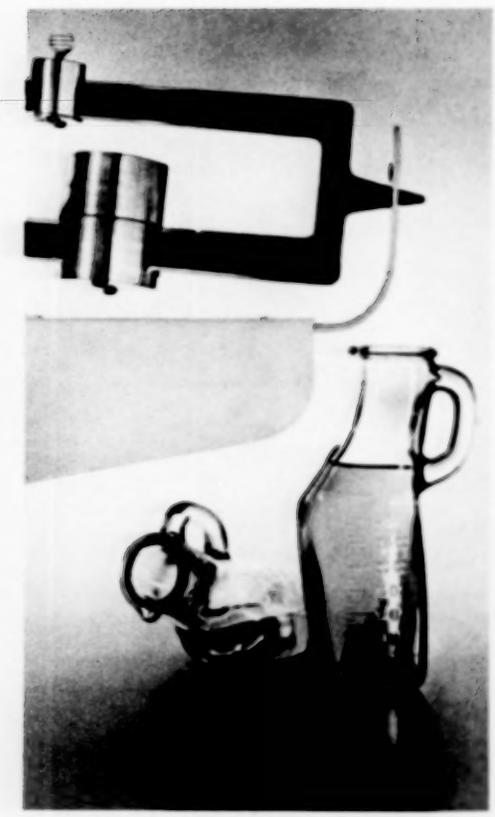
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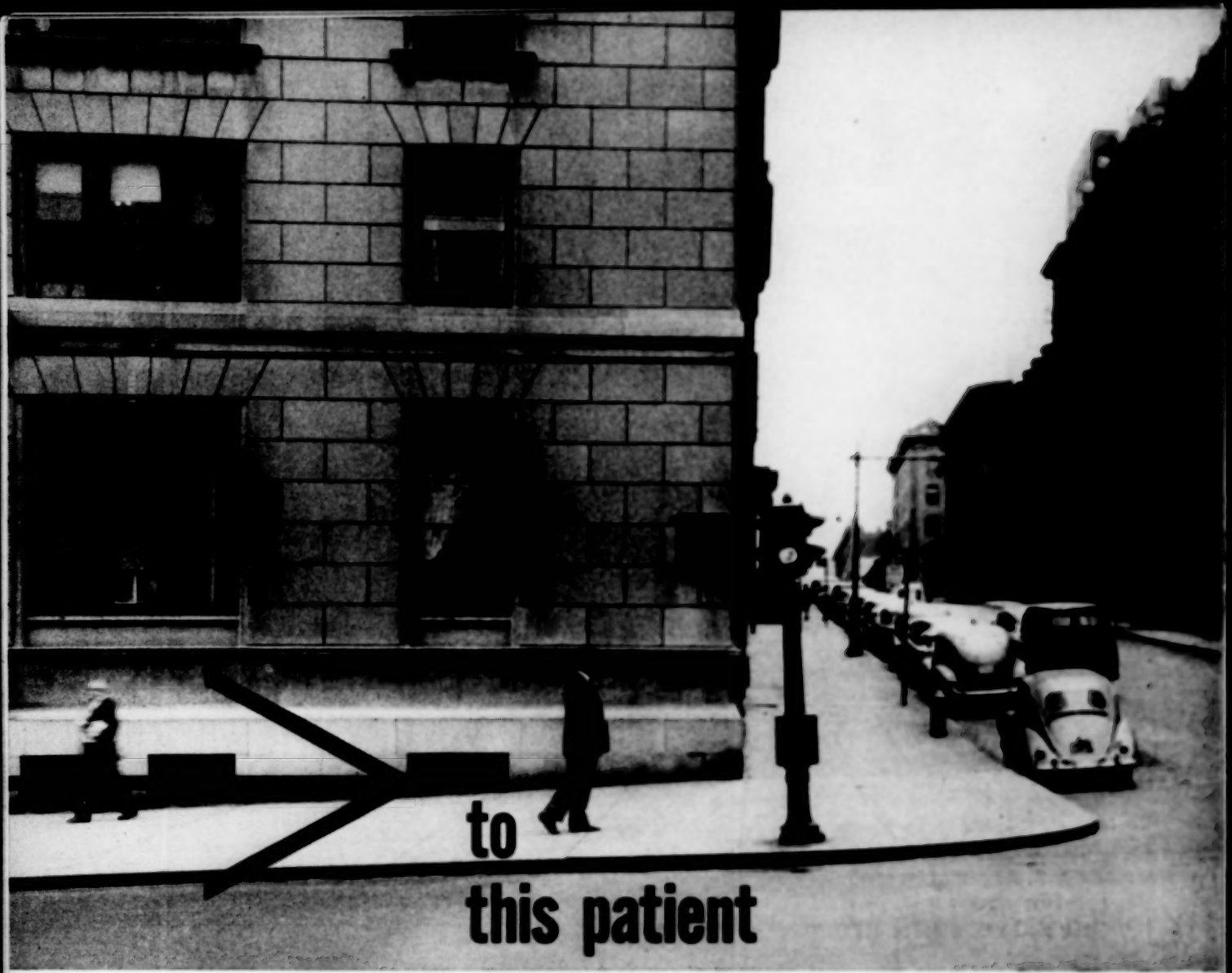
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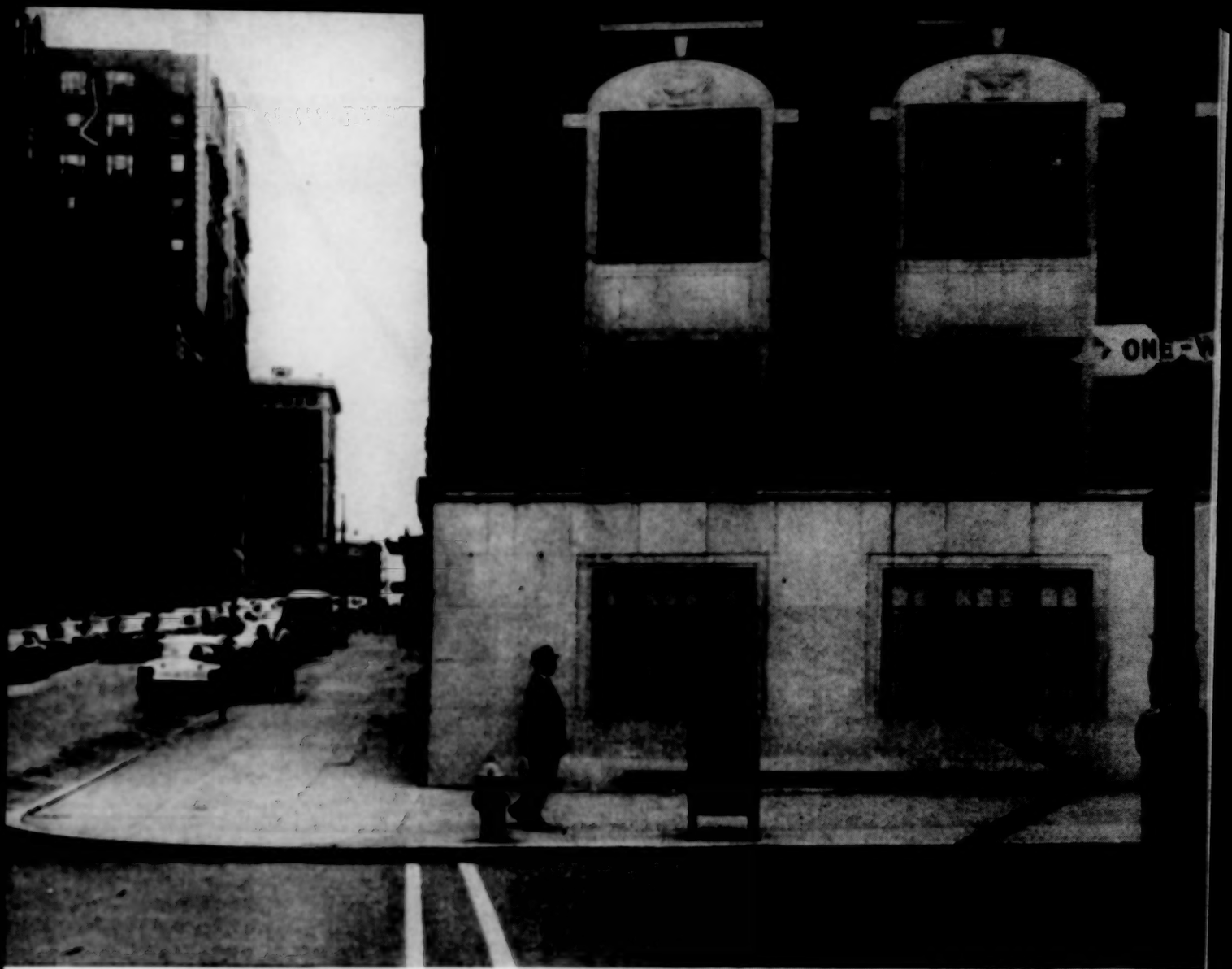
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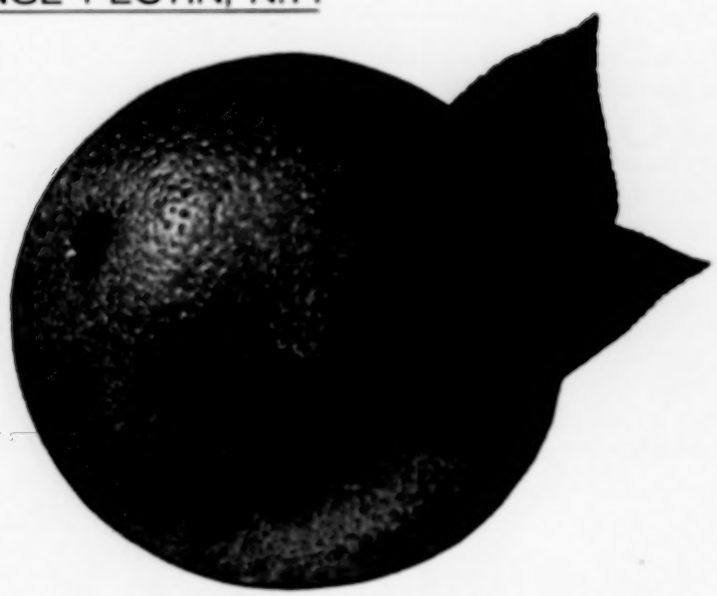
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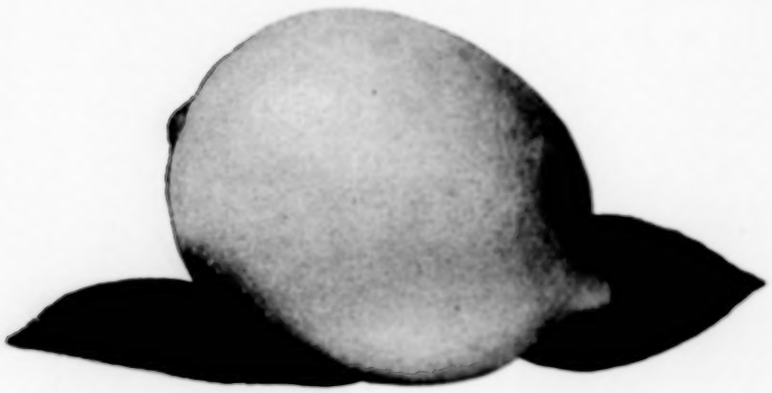
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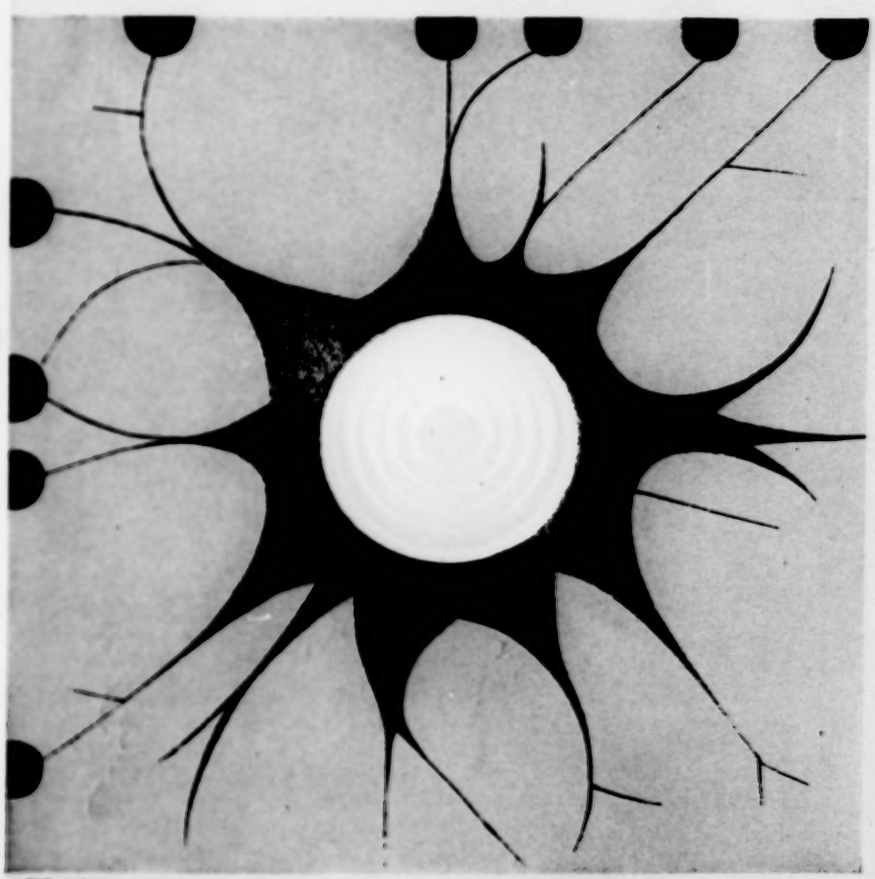
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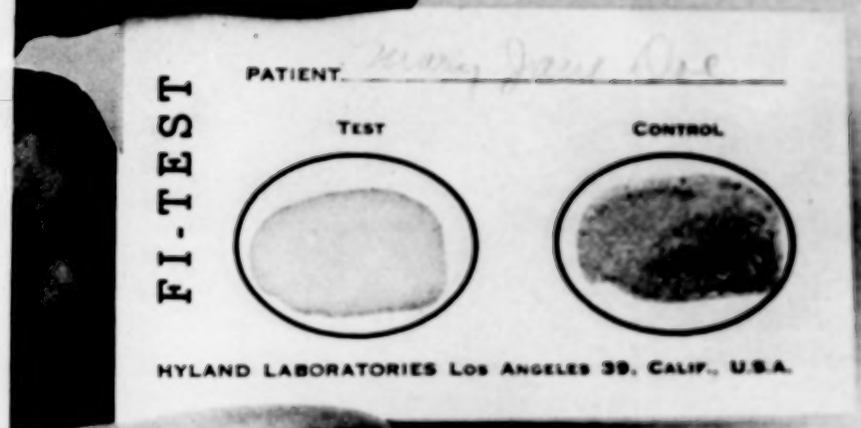


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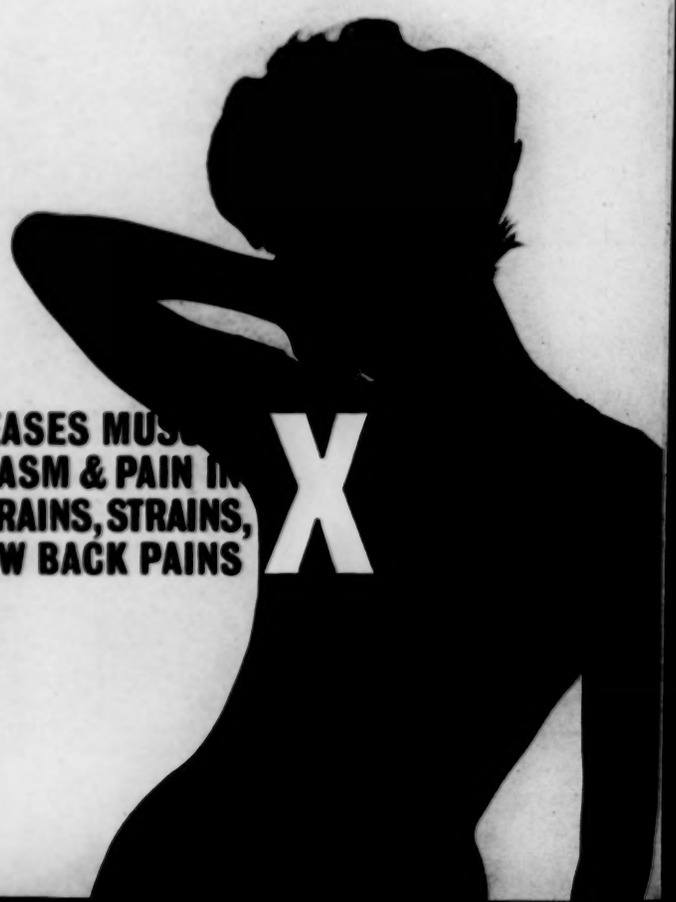
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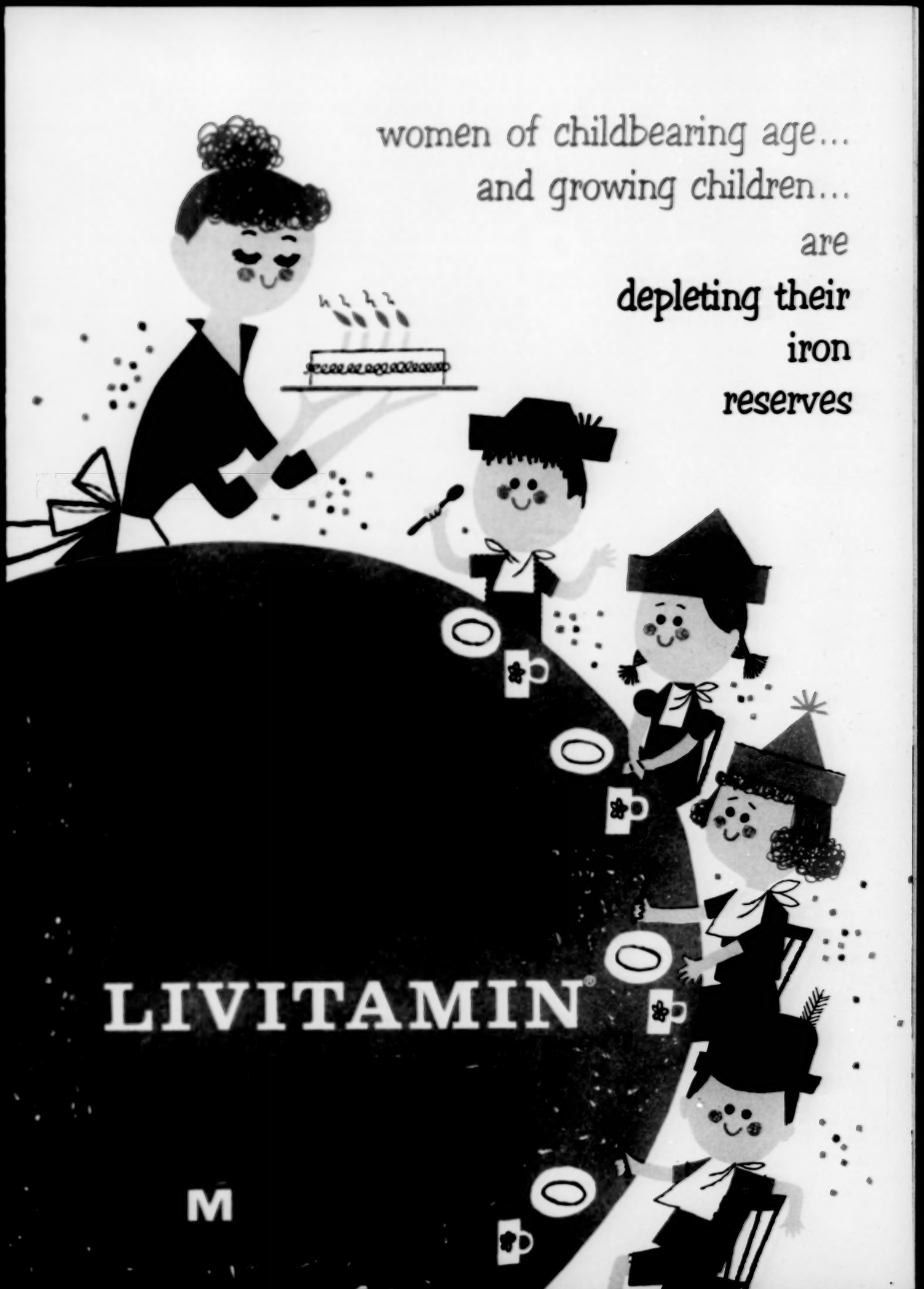
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1. Lehrer, H. W., et al.: Northwest Med. 75:1249, 1955.
2. Smith, Richard T.: New York Med. 8:16, 1952.

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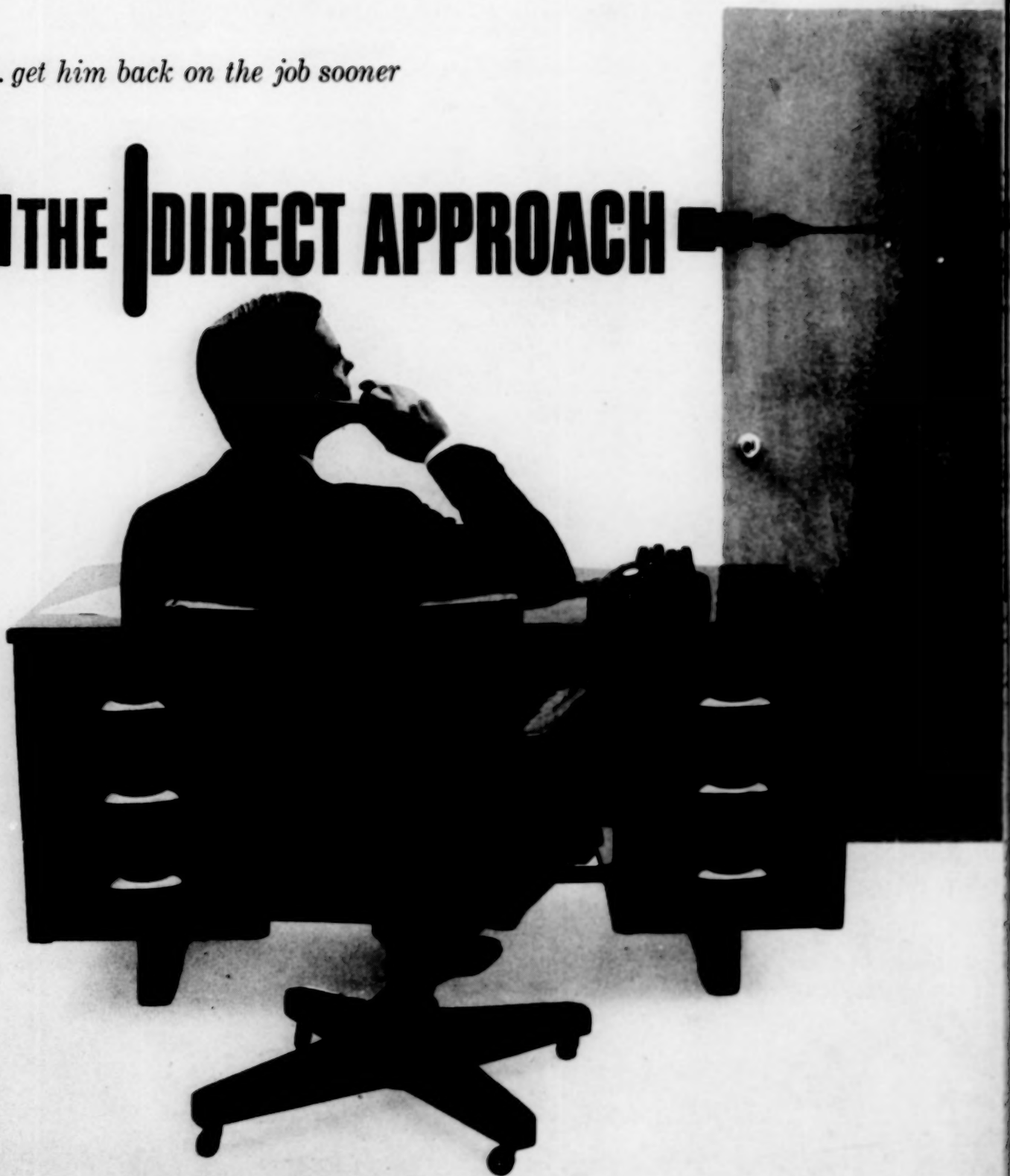
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1. Carmely, D. A., and Ritter, J. A.: N-acetyl-p-aminophenol (Tylenol Elixir) as a Pediatric Antipyretic-Analgesic, J.A.M.A. *160*:1219 (Apr. 7) 1956.
2. Minta, A. A.: Management of the Febrile Child, J. Ky. Acad. Gen. Pract. *5*:26 (Jan.) 1959.



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toses, and drug and serum reactions. POLARAMINE is the *anti*-histaminic which controls allergic reactions by effectively antagonizing the effects of histamine at therapeutic doses lower than those necessary with other available antihistamines.

Histamine is present in those body areas exposed to contact with the external environment: the skin, the upper gastrointestinal tract and the respiratory tree. For this very reason, if your patient develops a cold or illness with allergic complications, his symptoms are particularly troublesome. When an antigen provokes an antibody response, histamine is released, and the familiar symptoms of allergy follow. However, POLARAMINE can effectively control allergic symptoms.

POLARAMINE REPETABS (4 mg. and 6 mg. dosage forms for your patients' convenience) and POLARAMINE Tablets (2 mg.) are of unrivaled effectiveness and safety at doses lower than other antihistamines. Summarizing treatment of a recent group of 100 allergic patients, Babcock and Packard state that POLARAMINE REPETABS were "especially effective in patients who presented sudden, acute allergy symptoms."[1] Remember, too, that POLARAMINE Syrup (yes, it tastes good!) is very helpful in dealing with the young allergic patient or those preferring liquid medication.

Dosage: REPETABS, 6 mg. and 4 mg.—One REPETAB in the morning and one REPETAB in the evening. Tablets, 2 mg.—one t.i.d. or q.i.d.; children under 12, one-half tablet t.i.d. or q.i.d.; infants, one-quarter tablet t.i.d. or q.i.d. Syrup, 2 mg. per 5 cc. —Adults, one teaspoonful t.i.d. or q.i.d.; children under 12, one-half teaspoonful t.i.d. or q.i.d.; infants, one-quarter teaspoonful t.i.d. or q.i.d.

Supply: POLARAMINE REPETABS, 6 mg., bottles of 100 and 1000; 4 mg., bottles of 100 and 1000. Tablets, 2 mg., bottles of 100 and 1000. Syrup, 2 mg. per 5 cc., 16 oz. bottles.

1. Babcock, G., Jr., and Packard, L. A.: Clin. Med. *6*:985 (June) 1959.

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Albert[5] found that of 29 patients receiving ISORDIL, 25 responded well, 1 moderately well, and 1 not at all. Effectiveness could not be judged in 2 patients. For those who responded well, the frequency of anginal attacks was quickly reduced from a daily average of 5 to 1.2. Continued use of ISORDIL further reduced the frequency of attacks.

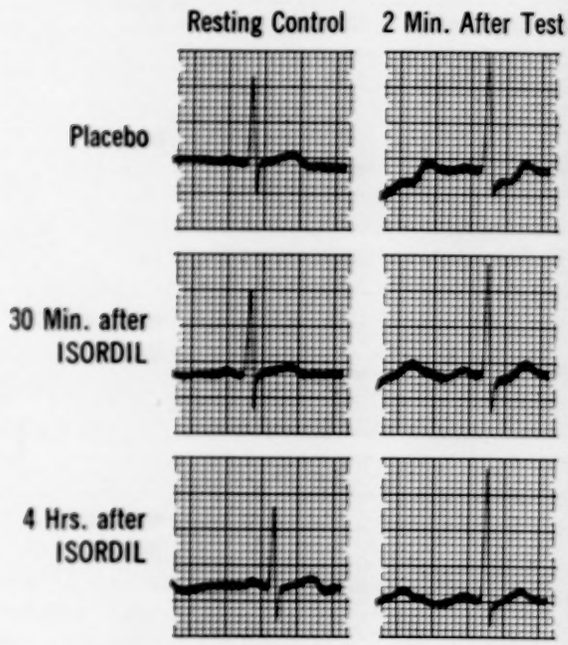
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Indications: ISORDIL is indicated for the therapeutic and prophylactic management of angina pectoris and coronary insufficiency. It is often useful in patients only partially responsive to other long-acting coronary vasodilators.

Dosage: ISORDIL is administered orally. Average dose is one tablet (10 mg.) taken one half hour before meals and at bedtime. Individualization of dosage may be necessary for optimum therapeutic effect; dosage may vary from 5 mg. to 20 mg. q.i.d.

Side Effects: Side effects are few, infrequent, and mild. Transitory headache, common to effective nitrate or nitrite therapy, has occurred. This usually responds to administration of acetylsalicylic acid, and disappears with continued therapy. When headache is persistent, reduction in dosage may be required.

Caution: ISORDIL should be given with caution in patients with glaucoma.

Supplied: Bottles of 100.

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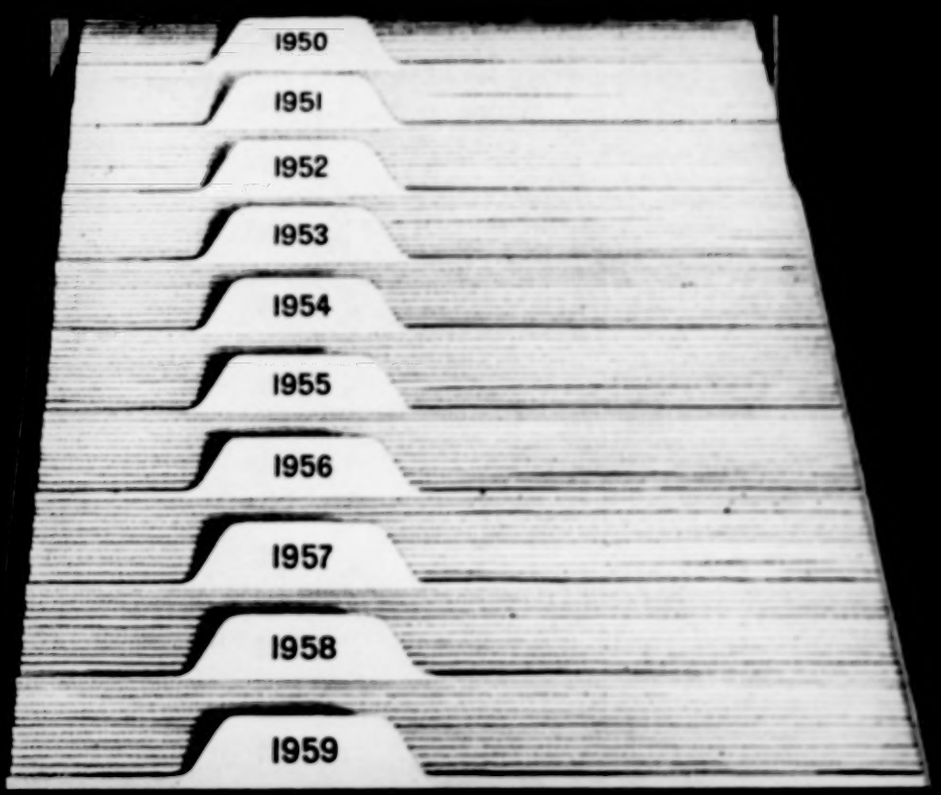
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2. Lockie, L. M., and Talbott, J.: Does Your Patient Have Gout?, Scientific Exhibit, American Medical Association, New York City, June 3-7, 1957.

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3. Kron, K. M., Hermann, I. F., Smith, R. T., and Richards, J. C.: Which Rheumatic Disease?, Scientific Exhibit, American Medical Association, Atlantic City, June 8-12, 1959.

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REFERENCES:

1-11. Papers read at Seventh Symposium on Antibiotics, Washington, D. C., November 4-6, 1959.

12. Phillips, F. M.: DECLOMYCIN—Seventh Interim Report. Department of Clinical Investigation, Lederle Laboratories, Pearl River, N. Y., December 4, 1959.

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urogenital infection. Vineyard, J. P.; Hogan, J., and Sanford, J. P.,[7] Dallas, Texas—Clinical response in pyelonephritis correlated well with results of *in vitro* sensitivity tests, which showed some strains of *A. aerogenes*, Proteus and Pseudomonas more susceptible to DECLOMYCIN Demethylchlortetracycline than to its analogues.

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1. Russek, H.I.: Am. J. Cardiol. *3*:547 (April) 1959.

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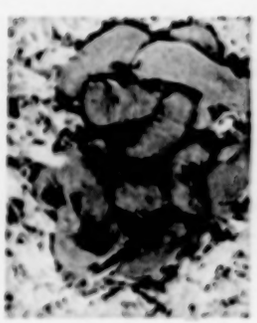
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CATRON is a monoamine oxidase (MAO) inhibitor useful in the treatment of depression and of other disorders indicated below. It is recommended for use in carefully selected cases and in those patients who have not responded to the milder drugs.

ADMINISTRATION AND DOSAGE:

Dosage of CATRON must be individualized according to each patient's response. The initial daily dose should not exceed 12 mg. and should be reduced as soon as the desired clinical effect is obtained. In severe depressions some clinicians desire rapid results and begin treatment with 24 mg. daily; this dosage should not be continued for more than a few days. A single daily dose in the morning is recommended. A continuous or interrupted schedule may be used, the latter during the maintenance period.

DEPRESSION (Endogenous, Reactive, Postpartum, Involutional, and Depression Secondary to Schizophrenic or Neurotic Reaction): initially, 12 mg. once daily for approximately 2 weeks, or less if improvement appears. Dosage is then reduced to 6 mg. daily. As improvement continues, maintenance dosage of 6 mg. every other day or 3 mg. daily often proves satisfactory. An interrupted dose schedule is recommended for long-term therapy.

ANGINA PECTORIS: 3 to 6 mg. daily in most cases. Relief of pain and elevation of mood may be dramatic. Victims of angina pectoris who respond in this manner should be cautioned against overexertion induced by their sense of well-being.

RHEUMATOID ARTHRITIS (Adjunctive Therapy—in severely disabling forms, particularly when accompanied by depression): 9 to 12 mg. daily for 3 days, then 6 mg. daily, reducing further to 3 mg. daily on signs of improvement. If a conventional antiarthritic agent is used, lower doses of each are indicated.

CAUTION:

Certain circumstances should be watched carefully when using CATRON.

DRUG POTENTIATION—The list of drugs which CATRON potentiates is not yet complete. Hence, caution should be exercised when combining CATRON with any other drugs such as tranquilizers, phenothiazines, the amphetamines, barbiturates, and hypotensive agents.

HYPOTENSIVE EFFECT—All normotensive patients receiving CATRON, but especially elderly patients, should be warned about the possibility of orthostatic hypotension during the initial period of higher dosage. In the few instances where this may occur, lowering of the dose will usually permit continuation of therapy.

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occur. In a few instances, at unusually high dosage, or where the drug was not discontinued following color disturbances, diminished visual acuity occurred.

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SIDE EFFECTS—Major side effects requiring cessation of therapy are infrequent. Other side effects—constipation, delay in starting micturition, increased sweating, hyperreflexia, ankle edema, blurring of vision, dryness of the mouth—are usually readily controlled by lowering the dosage. Rash, observed in a few patients, cleared up rapidly upon discontinuing therapy.

WARNING: Although pharmacologic evidence indicates that CATRON has a selectivity for the brain, it, as well as other monoamine oxidase inhibitors, may be associated with hepatitis. Because of the possibility of this life-threatening hepatitis, the following recommendations and precautions should be observed. If necessary, the patient should be hospitalized to expedite adherence to this regimen.

The Following Precautions Are Recommended:

1. In all instances daily dose should not exceed 12 mg.
2. Reduce daily dose as soon as response is established, usually in a matter of 1 to 2 weeks.
3. Do not prescribe to a patient more than sixteen 6 mg. tablets or thirty-two 3 mg. tablets of CATRON at one time.
4. Patient should return for observation before additional CATRON is prescribed. For this reason, prescriptions for CATRON should be marked "not refillable."
5. Perform regular liver function tests.
6. Do not use the drug in patients with a history of viral hepatitis or other liver abnormalities.

SUPPLIED: CATRON is the original brand of pheniprazine hydrochloride. It is supplied in tablets of 3 mg. and 6 mg., bottles of 50.

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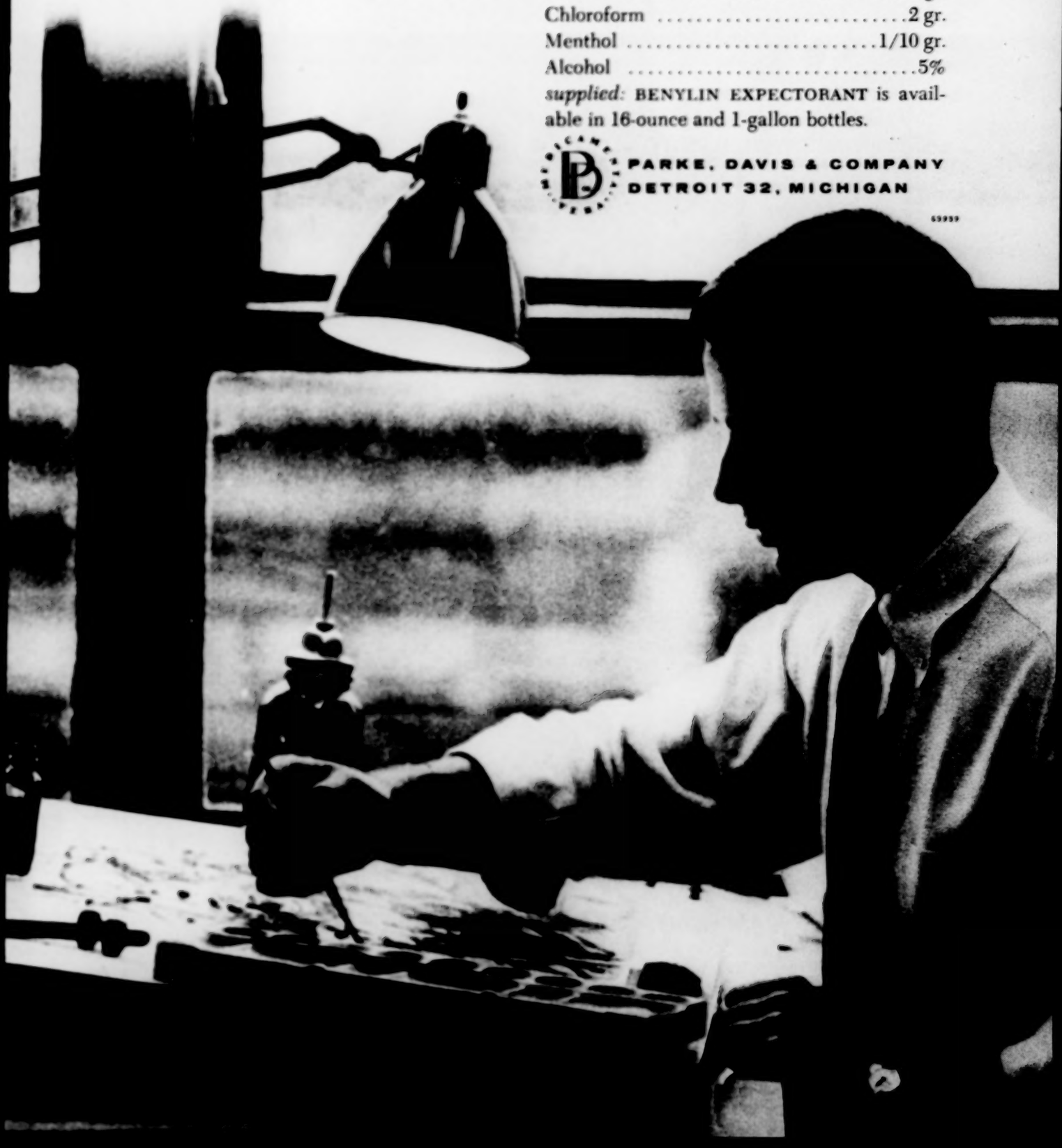
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